

A large, stylized, semi-transparent 'R' logo is positioned in the upper right quadrant of the cover. It consists of a solid circle on the left and a vertical bar on the right, with a curved line connecting them at the top. The background is a gradient of blue and purple with abstract light patterns.

# MODERN RHEUMATOLOGY

Volume 25 Supplement 2015

## ABSTRACT SUPPLEMENT

The 59th Annual Scientific Meeting  
JCR2015 Annual Course Lecture

April 23-25, 2015  
Nagoya

Japan College of Rheumatology

# JAPAN COLLEGE OF RHEUMATOLOGY ABSTRACT SUPPLEMENT

## CONTENTS

### ABSTRACTS

Presidential Lecture .....	S2
Representative Session .....	S2
Symposium .....	S3
International Symposium .....	S28
Educational Lecture .....	S31
Meet the Expert .....	S37
Specified Workshop .....	S42
International Concurrent Workshop Clinical .....	S45
International Concurrent Workshop Basic .....	S60
Workshop .....	S76
The Subcommittee on Gender Equality Support Program ..	S186
Anaphylaxis Guideline Program .....	S187
Poster Session .....	S188
Luncheon Seminar .....	S354
Evening Seminar .....	S365
Annual Course Lecture .....	S371
Annual Course Lecture Luncheon Seminar .....	S372

<b>AUTHORS' INDEX</b> .....	S373
-----------------------------	------

## Presidential Lecture

### PL

#### From human immunology to next generation rheumatology

Kazuhiko Yamamoto

Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo

Conflict of interest: Yes

The main subject of the 59th annual scientific meeting of JCR is “Toward next generation rheumatology”. As the presidential lecture, I would like to start by introducing my brief history of rheumatology research and then discuss “Next generation human immunology” as one of important research fields in rheumatology. Further I believe that “Next generation rheumatology” should have global perspectives. Thus, I would like to present my lecture in English in the same way as Prof. Takasaki at the last annual meeting. Our group started research projects on human rheumatic diseases in the mid-1980s using various molecular biology techniques. At first, we commenced molecular cloning of genes encoding the target molecules recognized by autoantibodies in patients followed by epitope analyses of the autoantigen molecules. As the results, we understood autoantibodies are generated by antigen-specific immune responses. If this is the case, antigen-specific T cells should play important roles. However, it was not easy to detect antigen-specific T cells in patients. We then developed a unique system to detect such antigen-specific T cells using a concept that antigen-specific T cells should proliferate with the stimulation of an appropriate antigen. With this system, we found clonally proliferated T cells in the peripheral blood of patients with rheumatoid arthritis (RA), which is quite distinct compared with those observed in healthy subjects. Further, synovial tissues of RA patients possess more extended accumulation of clonally proliferated T cells. It is also important to know that same clones are frequently observed in the different synovial tissues of different joints of the patient. We believe these findings will lead to a concept of antigen-specific next generation therapies. In order to identify diseases-associated genes, genome-wide association study (GWAS) is a promising strategy. We have been involved in such studies in collaboration with RIKEN. We recently reported 42 novel RA risk loci by trans-ethnic GWAS meta-analysis. Interestingly, although some susceptible single nucleotide polymorphisms (SNPs) affect an alteration of amino acid residues in the protein, majority of autoimmune associated SNPs were found to work as expression quantitative trait loci (eQTLs). An eQTL is a genomic locus that regulates the expression level of mRNA or protein. We believe that the combination of disease-associated polymorphisms and information of gene expressions would enable us to understand causative relationship between intermediate phenotypes such as gene expression and final diseases. This point of view could be a new concept of human immunology research and would thus contribute next generation rheumatology.

## Representative Session

### RS

#### Targeting Human Regulatory T Cells for Controlling Immune Responses

Shimon Sakaguchi

Immunology Frontier Research Center, Osaka University, Japan

Conflict of Interest: None

Naturally occurring regulatory T (Treg) cells, which express the transcription factor Foxp3, are indispensable for immunological unresponsiveness to self-constituents, i.e., self-tolerance, and immune homeostasis. They can be exploited to induce transplantation tolerance by expanding them in an antigen-specific fashion and to evoke effective tumor immunity by reducing them or attenuating their suppressive activity. To target Treg cells for these purposes, we have attempted to characterize subpopulations of human Foxp3<sup>+</sup> T cells, which included suppressive and non-suppressive populations. Our study has shown that Foxp3<sup>+</sup> cells can be separated into at least three functionally distinct subpopulations, including (1) highly proliferative and differentiated Foxp3-high population (designated effector Treg cells) with stable Treg-specific epigenome alterations, the majority of which will die by apoptosis after suppression, (2) naïve Foxp3-low population (naïve Treg cells), which is in a resting state and upon TCR stimulation differentiates into effector Treg cells, and (3) Foxp3-low non-suppressive population unstable in Treg-specific epigenome changes and capable of secreting pro-inflammatory cytokines. Each population exhibits distinct behavior in different disease states, and Depletion of effector Treg cells alone, by preserving naïve Treg cells, is sufficient for evoking tumor immunity without eliciting serious autoimmunity. In addition, naïve Treg cells can be expanded ex vivo by strong antigen stimulation in the presence of IL-2 and can be used for immune suppression. We will discuss how Treg subpopulations can be controlled for augmenting or suppressing a variety of immune responses in clinical settings.

## Symposium

### S1-1

#### Significance of mycophenolate mofetil in treatment for SLE

Daisuke Suzuki, Kumiko Shimoyama, Noriyoshi Ogawa  
Internal Medicine 3, Hamamatsu University School of Medicine, Hamamatsu, Japan

Conflict of interest: None

Corticosteroid therapy is a basic treatment for Systemic Lupus Erythematosus (SLE). Immunosuppressive agents are used with corticosteroid for refractory SLE. Cyclophosphamide (CY) is one of the most reliable drugs for severe SLE. On the other hand, it has significant adverse effects such as infertility and carcinogenesis. For this reason, we hesitate to use CY for younger patients, especially women. Maintenance therapy after CY therapy is another important problem. Safety and effectiveness are simultaneously necessary in immunosuppressive agents for SLE. Mycophenolate mofetil (MMF) is absorbed from intestines, and is converted into an active form; mycophenolate acid (MPA). MPA is inactivated in liver by glucuronic acid conjugation. Some part of MPA enters into enterohepatic circulation. MPA inhibits inosinemonophosphate dehydrogenase in de novo pathway of purine synthesis and suppresses lymphocyte proliferation. MMF induces apoptosis in activated T cells and suppresses antibody production from B cells. MMF has been proven to be efficient and comparatively safe in many clinical trials of induction and maintenance therapy for lupus nephritis. MMF is expected to be a substitute for CY. In Japan, MMF is not officially approved for SLE, however, its efficacy is gradually recognized. MMF can be used in combination with tacrolimus in some cases. MMF is in a phase three trial for lupus nephritis in Japan and expected to be used in the near future. We have used MMF in approximately forty SLE cases as a maintenance therapy. Some of the patients used MMF for more than ten years. Infection was more frequent than other adverse effects, however, severe infection was not very frequent. MMF therapy has good tolerability and usefulness as a maintenance therapy for SLE. We report our experience of MMF and discuss the significance of MMF in SLE treatment.

### S1-2

#### Treatment with Hydroxychloroquine for Systemic Lupus Erythematosus

Naoto Yokogawa<sup>1,2</sup>

<sup>1</sup>Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, Japan, <sup>2</sup>Japanese Hydroxychloroquine Study Group

Conflict of interest: None

The antimalarials, hydroxychloroquine (HCQ) and chloroquine (CQ), have comprised the first-line of treatment for SLE for decades and are considered to be especially effective against its musculoskeletal and cutaneous manifestations. Recently the benefits of antimalarials on various SLE outcomes such as prevention of damage accrual, reduction in the risk of thrombosis, hyperglycemia, hyperlipidemia, infection, and even mortality have been reported. Accordingly, in 2014 an international task force recommended that serious consideration be given to the adoption of hydroxychloroquine (HCQ) in particular as a regular treatment for SLE on the grounds of its lower retinal toxicity compared to CQ. In Japan neither HCQ, nor CQ is available due to the banning of the latter in the 1960's following cases of serious retinal toxicity. In order to encourage adoption of HCQ as a standard treatment for SLE, we organized a Japanese hydroxychloroquine study group recommending development of the drug to the Ministry of Health and Welfare in 2009. As a result, Sanofi K.K. initiated the first phase 3 study of HCQ in collaboration with Japanese hydroxychloroquine study group. The most serious side effect of HCQ is retinopathy potentially resulting in blindness. A recent study has reported the incidence of retinopathy reaching 1% after 5 years of treatment. However, early detection of the adverse effects of HCQ use can stem long-term ophthalmological damage. To this end, an ophthalmological examination before, and regular screenings during, the course of treatment should be performed to minimize the risk of retinopathy. Although the drug may be obtainable from overseas sources for private use, any unsupervised use should be strictly forbidden. In conclusion, the introduction of HCQ will become a milestone in the standardization of

SLE therapy in Japan. Formulating a treatment guideline, accessible to both physicians and patients, will undoubtedly facilitate the process.

### S1-3

#### Combined modality therapy for rapidly progressive interstitial lung disease with dermatomyositis

Takahisa Gono<sup>1</sup>, Hidenaga Kawasumi<sup>1</sup>, Yasuhiro Katsumata<sup>2</sup>, Yasushi Kawaguchi<sup>2</sup>, Hisashi Yamanaka<sup>1</sup>

<sup>1</sup>Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, <sup>2</sup>Department of Rheumatology, Tokyo Women's Medical University Hospital, Tokyo, Japan

Conflict of interest: None

Dermatomyositis (DM) is a systemic autoimmune disease characterized by dermatitis and myositis. Interstitial lung disease (ILD) frequently occurs with DM—30 to 60% of patients with DM also develop ILD. The main treatment for DM is administration of a corticosteroid. Recently, therapies combining corticosteroid with immunosuppressive agents or intravenous immunoglobulin have been used in patients with DM, primarily those who have the complications of severe muscle weakness or ILD. However, the prognosis remains unsatisfactory, as reflected in the 80% 5-year survival rate among patients with DM. Appropriate management of ILD is important for improving the prognosis of DM. In 1980, anti-Jo-1 autoantibody was discovered. Anti-Jo-1 is associated with the development of myositis and ILD. The clinical course of ILD is usually slowly progressive. On the other hand, it had been reported since the 1980s that rapidly progressive ILD (RP-ILD) can develop in patients with clinically amyopathic DM (CADM). RP-ILD with CADM was characterized by poor response to corticosteroid treatment and the complication of mediastinal emphysema, a fatal outcome. Anti-Jo-1 was not found in these CADM patients, and a useful predictive marker for the occurrence of RP-ILD remained unknown for DM/CADM. In 2005, it was reported that anti-CADM-140 autoantibody was strongly associated with the development of RP-ILD in DM/CADM. In 2008, it was found that anti-CADM-140 recognizes melanoma differentiation-associated gene 5 protein as an antigen. Around the same time, it was revealed that increased serum ferritin levels predict the development and severity of RP-ILD in DM/CADM. The discovery of these useful predictive markers for RP-ILD enabled early diagnosis and treatment of RP-ILD with DM/CADM. In this symposium, the present status and problems related to RP-ILD with DM/CADM will be reviewed. We will also discuss the next-generation therapy for RP-ILD with DM/CADM.

### S1-4

#### Therapeutic potentials of interleukin-6 blockade for systemic sclerosis

Masataka Kuwana

Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine

Conflict of interest: Yes

Systemic sclerosis (SSc) is a multisystem disease characterized by excessive fibrosis of the dermis and internal organs, and widespread microvasculopathy. There is no therapeutic strategy proven to modify the natural course of the disease, and prognosis is still devastating, especially in patients with severe internal organ involvement, such as lungs, heart, and gastrointestinal tract. Recent basic researches have identified a series of growth factors, cytokines, and chemokines as potential effectors in SSc pathogenesis. Of these, interleukin-6 (IL-6) is of particular interest because of its potential utility as a therapeutic target for SSc. In SSc patients, overproduction of IL-6 in the skin was observed in patients with diffuse cutaneous SSc (dcSSc), especially in those in the early disease stage. The highest IL-6 concentration in sera was also detected in patients with early dcSSc. The high IL-6 expression early in the course of dcSSc is associated with more severe skin involvement at 3 years and worse long-term survival. In addition, IL-6 blockade resulted in reduction of skin sclerosis and lung fibrosis in bleomycin-treated mouse model. Moreover, there are several case reports showing improvement of skin sclerosis and joint contracture after treatment with anti-IL-6 receptor antibody tocilizumab. A recent double-blind placebo-controlled trial of tocilizumab failed to show statistically significant difference in modified Rodnan total

skin score and forced vital capacity between groups, although there was a trend toward superiority of tocilizumab-treated group. Since overexpression of IL-6 is closely associated with positive CRP and/or thrombocytosis, inclusion of patients with apparent IL-6 signature may clarify the treatment benefit of tocilizumab. These multiple observations suggest that IL-6 blockade may hold promise as a therapeutic strategy for SSc.

## S1-5

### Effect of Extracorporeal Shock Wave Therapy on Digital Ulcers of Systemic Sclerosis

Tomonori Ishii<sup>1</sup>, Hideo Harigae<sup>1</sup>, Yasushi Kawaguchi<sup>2</sup>

<sup>1</sup>The section of Hematology and Rheumatology, Tohoku University Hospital, Sendai, Japan, <sup>2</sup>Institute of Rheumatology, Tokyo women's Medical University

Conflict of interest: Yes

Systemic scleroderma (SSc) is an autoimmune disease characterized by excessive deposition of collagen in the skin and visceral organs as well as vascular damage, including Raynaud's phenomenon. Raynaud's phenomenon results from digital arterial closure after cold exposure, and is thought to be related to vascular remodeling and endothelial signal imbalance. Digital ulcers are common and occasionally disabling manifestation of SSc, which develop due to narrowing and occlusion of the digital arteries and arteriole. Digital ulcers occur within 4 years of diagnosis in 65% of patients with SSc. In some patients, particularly those with limited cutaneous SSc, digital ulcers represent the primary functional limitation. Treatment of SSc is disappointing since it is impossible to modify the course of the disease, especially with regard to Raynaud's phenomenon and stenosis of the peripheral artery, which ultimately succeeds to digital ulcers. Since such ulcers are not caused by autoimmune factors or abnormal coagulation, immunosuppressive therapies and anticoagulants have shown little effect. Extracorporeal shock wave therapy (ESWT) is defined as a sequence of sonic pulses characterized by high peak pressure, fast pressure increase, and short lifecycle. First applied in 1980 for treatment of kidney stones, during the last 10 years, this technique has been found to induce immediate antalgic and anti-inflammatory effects together with long-term tissue regeneration and an increase in angiogenesis. Recently, ESWT was demonstrated efficacy in curing and re-epithelialization of diabetic neuropathic foot ulcers. Concerning these accumulated results, ESWT could have the potency to stimulate new vascularization and healing when applied to the skin of SSc patients with Raynaud's phenomenon and digital ulcers. The aim of this study was to investigate the efficacy and safety of ESWT for treatment of refractory skin ulcers caused by SSc.

## S1-6

### Biologics Therapy for Neuro, Intestinal and Vascular Behçet's Disease

Hiroto Kikuchi

Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan

Conflict of interest: None

The efficacy of infliximab (IFX) for refractory retinal uveitis with BD was first shown in Japan in 2007. However, the efficacy of IFX for specific types of BD has only been examined through accumulation of case reports and presentations. A large prospective study of IFX for each type of BD has yet to be performed. Neuro BD is classified as acute type and chronic progressive type (CPNB). CPNB involves chronic progression of ataxia, dysarthria and mental disorders. A significant increase in the cerebrospinal fluid IL-6 (CSF-IL6) level and brainstem atrophy on brain MRI are also found. CPNB is resistant to conventional treatment. Methotrexate (MTX) pulse therapy or MTX+IFX combination therapy has been found to decrease the CSF-IL6 level and to inhibit the decrease in score on the Wechsler Adult Intelligence Scale (WAIS). Long-term follow-up studies show no significant deterioration in CSF-IL6, WAIS score, and brainstem MRI, indicating inhibition of progression by administration of IFX. Several cases of successful treatment of acute neuro BD by tocilizumab, among other biologics, have also been reported. Intestinal BD is treated effectively by TNF-inhibitor therapy. Administration of

adalimumab for Crohn's diseases and ulcerative colitis is currently covered by insurance in Japan, and similar administration for intestinal BD is also covered. In use of TNF inhibitors for rheumatoid arthritis, it is frequently difficult to control disease activity of intestinal BD, but a sufficient initial dose seems to increase the efficacy. Vascular BD shows a good response to biologics, as shown in previous cases and our cases, particularly for inhibition of inflammation. However, vascular BD often complicates with pulmonary thrombosis embolism due to a high rate of development of deep vein thrombosis. Identification of effective anticoagulants for vascular BD for prevention of complications requires further investigation.

## S2-1

### Vitamin D compound

Jun Hashimoto

Department of Rheumatology, National Hospital Organization, Osaka Minami Medical Center

Conflict of interest: Yes

In 1983, active vitamin D (alfacalcidol) was approved for managing osteoporosis in Japan. Currently, many anti-fracture agents are available and it is almost possible to prevent osteoporotic fractures under appropriate intervention. Even in this anti-fracture era, vitamin D supplements or medications are essential steps that should be taken prior to embarking on other anti-fracture medication. Apart from the classic role of vitamin D, it is also characterized by pleiotropic effects on various organs and tissues. It was shown that vitamin D deficiency have an many ill conditions including type 2 diabetes mellitus, various cancers, atherosclerosis, hypertension, autoimmune disease, ischemic heart disease, falls, infection and incidence of hospital mortality. Osteoporosis is a skeletal disorder characterized by a reduction in bone strength, it is required, however, to maintain general health of individual patient. While, adverse effects of vitamin D treatment should be noted prior to medication of vitamin D. Laboratory signs of vitamin D toxicity may appear before symptoms are evident. These laboratory signs include hypercalcemia, hyperphosphatemia, suppressed parathyroid hormone, and hypercalciuria and can occur after overdose of vitamin D. Hypercalciuria can lead to increased risk for kidney stones and hyperphosphatemia is associated with atherosclerosis and soft tissue calcification. So, it is also fundamentally essential to avoid problems of both undertreatment and overtreatment by vitamin D for the totally positive benefit-risk-balance of anti-osteoporotic fracture intervention. Although there are very limited markers in standard clinical practice, we should evaluate at least the serum Ca, IP, urinary Ca, iPTH and renal function to prescribe the appropriate dose of vitamin D. Moreover, it should be noted that active vitamin D compound without self-regulation of activation is used in Japan unlike other countries where nutritional vitamin D supplement were used.

## S2-2

### The Light and Shadow of Bisphosphonate

Hiroshi Hagino

School of Health Science, Tottori University

Conflict of interest: Yes

Since bisphosphonates (BP) can reduce the incidence of fragility fractures including hip fractures in patients with osteoporosis, they have become the first-line drugs for the treatment of osteoporosis. Numerous clinical studies have shown that most oral BPs that were originally developed for once daily administration demonstrate equivalent, or non-inferior efficacy and tolerability with weekly and/or monthly dosing regimens. Monthly intravenous administration and weekly jelly are also available in Japan. Such BPs offer patients with osteoporosis a new dosage option that may improve convenience as well as treatment adherence in those who are having difficulty complying with the currently approved daily and weekly dosage regimens. There are two major concerns for BPs; atypical femoral fractures (AFF) and osteonecrosis of the jaw (ONJ). Recent survey of AFF in Japan showed 57.1% in patients with AFF administered BPs. Radiographic features for AFF such as localized periosteal reaction of the lateral cortex, and generalized increase in cortical thickness of the diaphysis had relationship to BP therapy. It is proposed that

patients receiving bisphosphonates who are not at high risk for fracture are potential candidates for a drug holiday, while in patients with low bone mineral density or previous history of fragility fracture, the treatment should be continued.

## S2-3

### Teriparatide

Toshitsugu Sugimoto

Internal Medicine 1, Shimane University Faculty of Medicine

Conflict of interest: Yes

The results of large clinical trial using teriparatide (TPTD) demonstrated increases in bone mineral density (BMD) and preventive effects on vertebral and non-vertebral fractures that were greater than those observed with bisphosphonates (BPs). TPTD formula for daily subcutaneous injection was approved as bone anabolic agent in 2002 in USA. The efficacy and safety of this formula were subsequently confirmed in Japan, and daily formula was approved in 2010, followed in 2011 by the approval of formula for weekly subcutaneous injection which was developed in Japan. Unlike the relationship between daily and intermittent administration of BPs, a clear difference is seen between daily and weekly TPTD in the mode of action on the bone in terms of parameters such as changes in bone metabolic markers. However, no clear difference in efficacy exists between two formulas and new strategies for fracture prevention, in which bone anabolic agents are added according to various disease states, are now available. TPTD is indicated for osteoporosis (OP) patients with high fracture risk, such as those with markedly decreased BMD, severe or multiple vertebral fractures. TPTD may also be expected to be effective for inadequate antiresorptive responders, male OP, secondary OP such as glucocorticoid-induced or diabetic OP and OP resulting from stage G3a chronic kidney disease. In addition, the efficacy for OP with low grade quality of life and severe back pain is also becoming established. On the other hand, though only a limited exploratory study at this point, reports are available about the usefulness of TPTD for atypical femoral fractures, osteonecrosis of the jaw, and fracture healing, indicating its utility in cases of OP in which there are concerns over non-union after fractures. Because the administration period is limited and BMD decreases rapidly following discontinuation, sequential treatments are being investigated, and the efficacy of BPs and denosumab is noteworthy.

## S2-4

### Denosumab

Sakae Tanaka

Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo

Conflict of interest: Yes

Osteoclasts are multinucleated giant cells primarily responsible for bone resorption. Osteoclasts are differentiated from monocyte/macrophage-lineage precursor cells in the presence of receptor activator of NF- $\kappa$ B (RANKL) and macrophage colony-stimulating factor. A number of studies have shown that RANKL-RANK pathways play essential roles in the pathologic bone resorption such as osteoporosis, rheumatoid arthritis, cancer bone metastasis and periodontal diseases. Denosumab, a fully human IgG2 monoclonal antibody that binds human RANKL with a high affinity, potently suppresses osteoclast development and reduces bone resorption. In a study of postmenopausal osteoporosis patients (FREEDOM), denosumab significantly reduced the risk of new vertebral fractures at 3 years by 68%, non-vertebral fractures by 20% and hip fractures by 40% relative to placebo. To examine the anti-fracture efficacy and safety of denosumab (60 mg subcutaneous injection every 6 months [Q6M]) in Japanese patients with primary osteoporosis, a randomized, double-blind, placebo-controlled trial with an open-label referential arm was conducted (DIRECT trial). Denosumab reduced the risk of new or worsening vertebral fracture, with incidences of 3.6% in the denosumab group and 10.3% in the placebo group in 24 months without increasing the risk of adverse events of interest. These results suggest that anti-RANKL therapy is effective in reducing osteoporosis fractures.

## S2-5

### SERM

Atsushi Suzuki

Division of Endocrinology and Metabolism, Fujita Health University School of Medicine, Aichi, Japana

Conflict of interest: Yes

Menopause dramatically changes hormonal profile in middle-aged women and postmenopausal life has become longer than before due to better life expectancy. Bone metabolism is well modified by sex steroid levels in both men and women, and the imbalance between bone resorption and formation results in bone loss. Hormone replacement therapy by estrogen is actually effective to prevent osteoporotic fracture in postmenopausal women, but its serious adverse effects including carcinogenesis in breast limits the use of estrogen for long-term protection against osteoporosis. Selective estrogen receptor modulators (SERMs) are diverse group of nonsteroidal compounds that act as agonists or antagonists in a target gene and in a tissue-specific fashion. As for therapeutic use of SERMs in osteoporosis, raloxifene is the first SERM clinically available. Raloxifene has enough potency to prevent vertebral fracture in postmenopausal women, though its efficacy for non-vertebral fracture including hip fracture is limited. Raloxifene is also effective at preventing breast cancer, and is not associated with, and may even be effective at, preventing endometrial cancer. Bazedoxifene acts as an estrogenic in bone and lipid metabolism and antagonistic in breast and endometrium. Bazedoxifene alone prevents vertebral fracture in postmenopausal women, and reduced the risk of non-vertebral fracture in those with higher risk of osteoporotic fractures. Bazedoxifene plus conjugated estrogens had reduced incidence of endometrial hyperplasia over placebo and a significantly increased bone mineral density in the lumbar spine and hip. In vivo data suggest us that SERMs might contribute to ameliorate bone quality in animal models such as diabetes, but its clinical impact has not yet been proven. The common adverse effects of SERMs are hot flashes, leg cramps and increased risk of blood clots. SERMs are beneficial tool to improve quality life and activity of daily life in postmenopausal women.

## S2-6

### Up and coming anti-osteoporotic drugs

Yasuhiro Takeuchi

Toranomon Hospital Endocrine Center

Conflict of interest: Yes

Alendronate as a prototype of nitrogen-containing bisphosphonates has been clinically available since 1990s and opened up the new era of treatment of osteoporosis. Alendronate has succeeded to decrease the incidence of osteoporotic fracture for the first time. Following the emergence of alendronate, several promising anti-osteoporotic drugs have become available; however, so far they could reduce the incidence of osteoporotic fracture only to approximately 50%. In addition, there remain some concerns about long-term use of bisphosphonates, for example, they might increase the incidence of atypical femoral fractures. Thus, we are waiting for the development of new classes of anti-osteoporotic drugs. Since many investigators have successfully explored molecular mechanisms whereby osteoporosis develops, several unique drugs that specifically modulate key molecules in bone metabolism are in the pipeline. The front runner among them is odanacatib, a cathepsin K inhibitor. The pivotal clinical study to demonstrate anti-fracture efficacy of odanacatib has been already completed. In order to promote bone formation, monoclonal antibodies against sclerostin that inhibits osteoblastic bone formation are also under development for clinical use. Romosozumab, one of anti-sclerostin antibodies, has been shown to robustly increase bone mineral density in postmenopausal women with low bone mass. It is currently on the way to confirm to reduce the incidence of osteoporotic fracture. We are surely going to have some more tools to overcome osteoporotic fractures in the near future.

## S3-1

### Therapeutic exercise

Hiroshi Ikeda, Yuji Takazawa, Muneaki Ishijima, Yoshitomo Saita, Haruka Kaneko, Youhei Kobayashi, Ryo Sadatsuki, Shinnosuke Hada

Orthopaedic Surgery, Juntendo University School of Medicine, Tokyo, Japan

Conflict of interest: None

Japan is heading rapidly toward aging of the population. 50 years ago, elderly persons aged 65 years or above constituted only 6% of total population. However, 25% of population are elderly persons now, and one-third will become elderly persons 20 years later. Proportional to the aging population, the incidence of aging-related bone and joint diseases also increases, and has become an important factor impairing the activities of elderly persons. Among these diseases, osteoarthritis are most prevalent. Especially, knee osteoarthritis (knee OA) is estimated to affect over 10 million persons in our country and the care of these patients poses a great burden on medical facilities. The treatments of knee OA can be broadly classified into conservative and surgical modalities. Conservative treatments include pharmacological therapy such as nonsteroidal anti-inflammatory drugs (NSAIDs), physiotherapy, and therapeutic exercise. Surgical options include osteotomy and total knee arthroplasty. However, only a small proportion of patients require surgeries while the majority undergo conservative treatments. NSAIDs are commonly used for pain control, but adverse drug reactions are a concern in the predominantly elderly patients, and safer therapies are desired. On the other hand, therapeutic exercise is practical and has various merits; home-based exercise can be performed safely by the patient him/herself, and this method has economical advantage by reducing medical expenditure. The methods of therapeutic exercise include muscle strength exercise and walking exercise. Among them, the effectiveness of muscle strength exercise has been reported by multicenter clinical studies conducted mainly in America and Europe from the 1990s, and this method has established a status as the primary treatment within the therapeutic system of knee OA. We report the efficacy and limitation of therapeutic exercise for knee OA based on the results of clinical studies that conducted in our facility.

### S3-2

#### Drug treatment for osteoarthritis

Harumoto Yamada, Kazue Hayakawa, Mitsuhiro Morita, Hideki Date, Makoto Kato

Department of Orthopaedic Surgery, Fujita Health University

Conflict of interest: None

Osteoarthritis (OA) is caused by pathologic changes including cartilage destruction, secondary synovitis, repair process and accelerated remodeling of subchondral bone. It is difficult to determine the key molecule in OA pathology. All drugs now available clinically belong to symptom modifying drugs which decrease clinical symptoms including pain. Articular cartilage lacks receptor for pain, and secondary synovitis and bone edema are thought to be responsible for pain in OA. NSAIDs and corticosteroid are used to decrease secondary synovitis clinically for OA therapy, however acute increase of joint destruction due to suppression of pain should be monitored carefully. Bisphosphonate were used to cure bone edema and increase of bone remodeling in OA, however no significant clinical effects were reported. Duloxetine, which is one of SNRI was used in clinical trial for OA, and significant improvement of pain and WOMAC score was reported. Intraarticular injection of platelet-rich plasma which was collected from patient did not improve clinical symptom of OA patients. Development of several disease modifying drugs has been done. IL-1 and TNF- $\alpha$  are thought to play significant role in OA pathology. However, monoclonal antibodies against these cytokines did not improve clinical symptom and joint destruction in several OA trials. Strontium ranelate, which has been clinically used for osteoporosis treatment mainly in Europe, has used clinical trial for OA, and shown to have significant effect for pain relief and also suppression of joint destruction. Tanezumab, which is the monoclonal antibody against nerve growth factor (NGF) has been use for clinical trial for OA, however severe increase of joint destruction is noticed. Suppression of joint space narrowing is necessary to show significant anti-OA effect. Long term clinical trial for number of patients are necessary. Biological markers are expected to play significant role in the evaluation of anti-OA drugs in clinical trials.

### S3-3

#### Update of hyaluronan injection therapy in the treatment strategy of osteoarthritis

Takeshi Muneta

Tokyo Medical and Dental University

Conflict of interest: None

Hyaluronan (HA) injection product for osteoarthritis (OA) has been developed 27 years ago in Japan. Since then, 10 million vials per year were averagely used for patients with knee OA, etc. The safety and usability is thought to be established. However, international assessment on the guide lines shows that the evidence level of hyaluronan injection for knee OA has been decreased. One of the reasons of the lower evidence is in the mixed-up of many kinds of hyaluronan compound as a hyaluronan inclusively. The other reasons are in the indication for the hyaluronan injection therapy and the usage instructions. Also, any high-evidence study which clarify the usefulness of the HA injection has not been reported from Japan where the HA injection therapy is very popular and frequently used with relatively unlimited indication. The balance between efficacy and complications will be important with consideration of clinical usage of HA injection. The difference of molecular weight of HA seems not easily related to clinical efficacy. The better selection of HA compound will not be easily determined in each case. The HA injection indication itself is not so easy. A patient with severe knee pain with little OA change is not inclined to be a good candidate for HA injection from my clinical experiences. Diagnosis of knee pain of patients with OA is very important. In that sense, HA injection around the joint should be considered and understood better. The other purpose of HA injection will help preserving articular cartilage for longer period. The efficacy of HA injection for the cartilage preservation has not been well understood and elucidated. The effective usage of HA injection should be clarified and spread globally.

### S3-4

#### Neuronal mechanism based OA pain treatments

Takahiro Ushida

Multidisciplinary Pain Center, Aichi Medical University

Conflict of interest: Yes

From the epidemiological survey, 24 million of Japanese peoples are estimated to have radiological knee osteoarthritis (OA) and 8 million are estimated to have knee pain due to OA. Thus, population of OA is extremely high and its associate ADL disturbances are nationwide problem. As for the OA treatment, several options (exercise therapy, medication, joint injection, surgical intervention) have been developed and utilized but therapeutic outcomes are not always enough in many cases. Concerning about OA pain mechanisms, pain signal occurred from local nociceptor transmit to brain through peripheral nerve and spinal cord. In this pain pathway, dorsal root reflexes and axonal reflexes have important to generate neurogenic inflammation and this mechanism may have important role in development/maintenance of joint pain. Also it is noted that dysfunction of descending spinal pain inhibitory pathway may underlying OA pain situation. These information suggest that manipulation of neuronal pathway potentially have therapeutic outcome in OA pain/disturbance. Under this concept, we introduced nerve blocks and anticonvulsants for OA pain cases and resulted fair pain relief by this treatment. As for other treatment option we developed focused ultrasound therapy to degenerate local nociceptor in knee OA cases. In several cases, long lasting pain reliefs were achieved by eliminating mal-circuit of pain pathway. In conclusion, we have to develop newer neuronal mechanism based less invasive OA treatment as well as OA prevention since so many population have potentially become OA situation in elderly.

### S3-5

#### International and Japanese treatment guidelines of osteoarthritis

Hiroshi Kawaguchi

Japan Community Health Care Organization (JCHO), Tokyo Shinjuku Medical Center

Conflict of interest: None

There are three representative international treatment guidelines for osteoarthritis (OA), each of which has different characteristics: Osteoarthritis Research Society International (OARSI), National Institute for Health and Clinical Excellence (NICE) from NHS in UK, and American Academy for Orthopaedic Surgeons (AAOS). Among them, the OARSI guideline is most frequently revised and has kept providing us with new evidence. Besides these international guidelines made by Western countries, there is a Japanese OA treatment guideline which was created by the Japanese Orthopaedic Association based on the OARSI guideline (part II). In some aspects, both guidelines are very similar; however, these guidelines showed a substantial difference, especially hyaluronic acid injection and supplements like glucosamine and chondroitin sulfate. In this lecture, I also introduce the newest 2014 OARSI treatment guideline (part IV) in which I was a committee member as the Asian representative, and discuss the present status of OA treatment in Asian countries. In addition, I will refer to the NICE guideline and the AAOS guideline.

#### S4-1

##### Treatment strategies for achieving complete remission in rheumatoid arthritis

Kazuyoshi Saito, Yoshiya Tanaka

The First Department of Internal Medicine, University of Occupational & Environmental Health, Fukuoka, Japan

Conflict of interest: Yes

The diagnosis and treatment strategies in the rheumatoid arthritis (RA) accomplished remarkable progress during recent 10 years. In 2010, ACR/EULAR proposed new RA classification criteria to classify patients with progressive arthritis and introduce methotrexate-based therapy in early stage disease and the algorithm of the treatment strategy was established as of T2T. Treatment aiming at clinical remission, structural remission, functional remission became a realistic target. However, in spite of such a medical progress, we can provide complete remission to only a small proportion of patients. In order to achieve a clinical remission to all of the patients who wish to be free from arthritis as soon as possible, rheumatologist should overcome a lot of issues for next stage of treatment of RA. Our ZERO-J study imply us that rapid dose escalation of MTX to 12-16mg /w within 3 months is needed for sooner resolution of synovitis and avoidance of unnecessary introduction of biologics. With biologic and non-biologic options, there is a need for strong predictive biomarkers including soluble factors, expression of surface molecules on lymphocytes, analysis of genomic DNA, to determine which drug is most likely to be effective, safe, and durable in a given individual. Also appearance of other biologics and small molecules which targeting to new molecules is dispensable for the patients who do not respond to several kinds of biologics. So far now, new drugs targeting fractalkine, GM-CSF-R, IL-17A, cyclin-dependent kinase, JAK, histamine receptor have been created and under trials for RA treatment. Management of RA after consistent clinical remission should be discussed. Free-J study is conducted to examine the way to de-escalation of treatment for attaining treatment holiday after achieving clinical remission as a multicenter clinical study.

#### S4-2

##### TLR-Targeted Lupus Therapy ~ the theory and the barrier ~

Hirofumi Amano

Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine

Conflict of interest: None

Toll-like receptors (TLRs) are associated with innate immunity, also with various diseases including systemic lupus erythematosus (SLE). TLR7, 8 sense ss-RNA, and TLR9 sense unmethylated CpG-DNA and are implicated in the development of SLE. The connection of these TLRs with SLE originates mainly from mouse models, where TLR7 signaling seems to play a central role. TLR7 gene duplication is the cause for the development of lupus in BXSB mice bearing the Y chromosome-linked autoimmune accelerating (*Yaa*) locus that harbors 17 genes, including TLR7. Although TLR7 play important roles in autoimmunity, C57BL/6 (B6). *Yaa* mice do not develop lupus phenotype. This means lupus phenotype related with *Yaa* mutation is requisite for autoimmune back-

ground. FcγRIIb and SLAM family member genes located in chromosome 1 are known as lupus susceptible genes. When the inhibitory FcγRIIb is substituted for wild-type B6 in BXSB. *Yaa* mice, the disease features were markedly suppressed. Accordingly with our other study results, the epistatic interaction of FcγRIIb deficiency and autoimmune-type SLAM haplotype seem to play major role for autoimmunity in the presence of *Yaa*-mutation. Hydroxychloroquine have been used for a long time in the SLE treatment. In recent years, many studies revealed that the drug act as TLR7/TLR9 inhibitor. More specific antagonist for TLR7/8 and TLR9 develop as a new therapy for SLE. IMO-3100, an antagonist of TLR7 and TLR9, is on the clinical trial for psoriasis and it is expected to use for SLE. Although the recent progress on the TLR-targeted therapy, it is not known the certain efficacy of these drugs to control the variable lupus phenotype including multiple organ damages. We speculate the need for the combination targeted therapy of Fcγ receptors and TLRs.

#### S4-3

##### BCAA for treatment of underpowered muscles during glucocorticoid healing of polymyositis and dermatomyositis

Akito Takamura<sup>1</sup>, Yoko Yoshihashi<sup>1</sup>, Naoki Kimura<sup>1</sup>, Michi Tanaka<sup>1,2</sup>, Ryuji Koike<sup>1,2,3</sup>, Kimito Kawahata<sup>1</sup>, Hitoshi Kohsaka<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, <sup>2</sup>Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, <sup>3</sup>Clinical Research Center, Tokyo Medical and Dental University Hospital of Medicine

Conflict of interest: Yes

Polymyositis (PM) and dermatomyositis (DM) are systemic autoimmune diseases that are characterized histologically by chronic inflammation and injury of the striated muscles and clinically by progressive muscle weakness. Glucocorticoids (GC) are used as the first line treatment of PM/DM while immunosuppressive agents are often used for cases refractory to GC. Although these drugs are effective for resolving muscle inflammation and subsequent muscle injury, they could not always improve muscle strength or activities of daily living (ADL) of some patients. It is because it takes some time for the muscle strength to recover after resolution of the inflammation, and high-dose GC may induce steroid myopathy. However, there are no therapeutic agents which have a direct effect to improve the muscle weakness. Branched-chain amino acids (BCAAs) are essential amino acids, which promote muscle protein synthesis and increase muscle mass in healthy subjects. Using animal models, it was revealed that BCAAs improve the muscle atrophy and weakness induced by the inflammation and GC. To investigate the effects of BCAAs for the muscle strength in PM/DM patients, we have started an investigator-initiated clinical trial named BTOUGH (BCAA for Treatment Of Underpowered muscles during Glucocorticoid Healing of polymyositis and dermatomyositis). In this double-blind, multicenter, randomized clinical trial, patients with untreated PM/DM will be randomly assigned to receive either BCAAs or placebo with conventional treatments using GC and immunosuppressive agents. The primary endpoint is the difference between MMT (manual muscle testing) scores at the beginning and after 12 week treatment. Muscle power measurement with hand held dynamometers, functional index, and timed stand test will also be used to assess the muscle strength and function. In this presentation, we will discuss and summarize recent findings of the role and effects of BCAAs in myositis, and introduce the BTOUGH study.

#### S4-4

##### Scleroderma Renal Crisis: pathophysiology and regulation

Hirahito Endo

Department of Rheumatology, Jusendo General Hospital, Fukushima, Japan

Conflict of interest: None

Scleroderma Renal Crisis (SRC) is an infrequent but life-threatening complication of systemic sclerosis (SSc). It was previously associated with significant morbidity, including chronic renal failure and dialysis therapy, and high mortality. Since the advent of angiotensin converting



enzyme (ACE) inhibitors, the outcome of SRC has improved dramatically. In addition, recent retrospective data in patients with SRC suggested that ACE inhibitors prior to the onset of SRC may have worse outcomes than those not taking drugs. SRC typically caused an acute onset of marked hypertension complicated with renal failure. SRC are most common in diffuse cutaneous SSc and short disease duration under 4 years. Other significant renal conditions, thrombotic microangiopathic hemolytic anemia (TMHA) and ANCA associated glomerulonephritis need to be considered as well. These patients sometimes showed a normotensive or a moderate hypertensive renal failure. SRC revealed the narrowing or obstruction of renal arteries which internal hyperplasia of arteries in kidney. SRC linked to presence of RNA polymerase III and absence of anti-centromere antibody. The increased synthesis of renin, although not shown to be a predictive biologic marker of SRC, progress hypertension complicated with renal failure. Aggressive treatment of hypertension in SRC is essential to prevent the occurrence of irreversible renal vascular injury. ACE inhibitors significantly improved blood pressure for many SRC patients. Evidence is growing for a role of dysregulation in the endothelin system in patients with SRC. A small open-label study using bosentan in patients with SRC was reported. Patients with SRC may recover renal function within 3 years, although mortality is highest in those who did not recover of renal function. We need a new therapeutic drug for suppressing the progress early stage of renal vessel lesions in patients with SRC.

#### S4-5

##### The prediction and treatment on difficult or severe cases of adult Still's disease

Toshihide Mimura

Department of Rheumatology and Applied Immunology, Saitama Medical University, Saitama Japan

Conflict of interest: None

Adult Still's disease (ASD) is an unknown systematic inflammatory disease, which shows characteristic symptoms including high fever, skin rash, polyarthritis and elevation of inflammatory cytokines in serum. The standard treatment may be a medium dose of oral glucocorticoid and the response, in general, is reasonably well, however, a part of the patients may exhibit poor response against the induction therapy or serious conditions in the disease course. Recently the research group for autoimmune diseases of the Ministry of Health, Labor and Welfare of Japan has conducted a nationwide survey of ASD between 2010 and 2011 to estimate the number of ASD patients in Japan and to assess the clinical manifestations, treatment, course, and prognosis of this disease. In this symposium some of the data from the survey will be presented. The estimated number of the patients in Japan was 4760 from the primary survey. The number of relapsed cases out of 169 reported patients in the secondary survey was sixty-six. Univariate analysis showed that lymphadenopathy, and complication of macrophage activation syndrome (MAS) were associated with risk of relapse in patients with ASD, however, marked hyperferritinemia ( $\geq 3,000$  ng/mL), complication of DIC, and medications of induction therapy were not. Multivariate analysis identified lymphadenopathy as the only significant factor for risk of relapse (OR=2.40, 95%CI 1.08–5.33;  $p=0.032$ ). Logistic regression analyses were conducted to explore potential predictive factors for complication of MAS, a representative serious condition in ASD. Significantly associated with complication of MAS were AST (OR=1.84, 95%CI 1.24–2.74;  $p=0.003$ ), LDH (OR=5.07, 95%CI 1.98–12.97;  $p=0.001$ ) and hyperferritinemia (OR=4.36, 95%CI 1.30–14.68;  $p=0.017$ ). Addition of immunosuppressants on the regular glucocorticoid may be one of the effective treatments for difficult or severe cases. Biologics may be more effective as the second-line therapy

#### S5-1

##### The Zen of Spondyloarthritis

David Yu

University of California Los Angeles, Los Angeles, USA

Conflict of interest: None

Although SpA is a rare disease in Japan, the history of how human beings endeavor to capture its essence is a superb lesson in human rea-

soning. Since Bekhterev first described AS in 1983, the alleged entity of SpA has been morphing her colors like a chameleon, adapting continuously from assaults by demands of patients, physicians, scientists and society. It has defied a strict definition despite the plethora of criteria organized by meetings of the minds in Rome, New York and finally globally. To supplement these criteria, investigators attempt to impose their "expert" points of view using expert-orientated guidelines, recommendations and consensus opinions. The situation appears even more complex to practicing physicians who do not carry the memory power to exercise BASDAI, ADAS etc at their fingertips. Their first challenge is to extract the tiny percentage of SpA out of the ocean of mechanical low back pain. Lacking diagnostic criteria, and being too inundated by "diagnostic" algorithms, most physicians rely on their own judgment. They are tempted to substitute discipline with representative-driven recommendations to use biologics, pushing the health care cost in Japan to exceed even 10% of the GDP. While global manufacturers are widening their indications of use of biologics to push their products into the top ten best selling drugs, local manufacturers are capitalizing on this opportunity for biosimilars. The pharmaceutical in Japan is the second largest in the world, and has 10% of the world market. Sitting at the tip of this human iceberg of endeavors are the patients. Among the sources of their discontent are anxiety, depression, loss of body image and fear of living. From the point of view of physicians, empathy and putting themselves in the shoes of their patients are not part of the curricula in their training. Thus, SpA is facing an immense challenge at the dawn of the 21st century.

#### S5-2

##### Psoriatic arthritis: the role of rheumatologists in the diagnosis and treatment

Atsuo Taniguchi, Naomi Ichikawa, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: None

Psoriatic arthritis is an inflammatory arthritis with psoriasis and is classified within spondyloarthritis. Five different subtypes (DIP predominant arthritis, asymmetric oligoarthritis, symmetric polyarthritis, axial disease predominant with spondylitis, and arthritis mutilans) are recognized and benign prognosis of psoriatic arthritis has been reported previously. However, recent studies revealed that the disease burden of psoriatic arthritis was comparable to those of rheumatoid arthritis and ankylosing spondylitis. In Japanese, the prevalence of psoriasis has been reported to be ~0.1% that is much lower than those of Caucasians. Therefore, the prevalence of psoriatic arthritis is lower than that of Caucasians and may not be a major disease in arthritis clinic. However, psoriatic arthritis has characteristic comorbidities and is one of the diseases with inflammatory low back pain. Furthermore, the recent investigation revealed the role of early diagnosis. One of the unique features of psoriatic arthritis is that arthritis usually follows the skin lesion. Therefore, patients with psoriasis are a high-risk group of the development of psoriatic arthritis. To screen the psoriatic arthritis in the patients with psoriasis in the dermatology clinic, some screening tools have been developed. These tools may be useful for identifying individuals with arthritis, however, absolutely do not superior to a rheumatological examination to make a diagnosis. Diagnosis of psoriatic arthritis may be made easier by the recognition of the characteristic features of psoriatic arthritis, including arthritis on DIP joints, an asymmetric distribution of arthritis, spondylitis and sacroiliitis, dactylitis, and enthesitis. The rheumatologist should manage joint disease of patients with psoriasis and cooperation with dermatologists will facilitate optimal management.

#### S5-3

##### What is "Inflammatory back pain"?

Shigeyoshi Tsuji

Department of Orthopaedic Surgery, National Hospital Organization, Osaka Minami Medical Center, Osaka, Japan

Conflict of interest: None

Although back pain in general is a common complaint in daily clinical practice, back pain due to SpA is comparatively uncommon and can frequently be distinguished from other causes of axial pain. Generally,

the back pain of SpA is termed “inflammatory back pain,” while back pain from other causes is termed “mechanical back pain.” Clinical features of inflammatory spinal disease include the following: onset before the age of 40 years, insidious onset, improvement with exercise, no improvement with rest, and pain at night. The Axial SpA of ASAS (the Assessment of SpondyloArthritis international Society) criterion was reported in 2009. The criteria included “Image evaluations of sacroiliac joint”. After the ASAS criteria were reported, “Time lag for diagnosis of SpA” was decreasing. The ASAS criteria contributed to a diagnosis of Axial SpA. But the ASAS criteria do not described “evaluations except SI joint”. We experienced a lot of cases of SpA with positive finding of MRI in axial involvement except SI joint. Now I would like to talk about “Inflammatory back pain”

#### **S5-4**

##### **Reconsider the ASAS classification criteria of spondyloarthritis~Non-radiographic SpA in daily practice~**

Mitsumasa Kishimoto<sup>1</sup>, Shigeto Kobayashi<sup>2</sup>, Yoshinori Taniguchi<sup>3</sup>, Tetsuya Tomita<sup>4</sup>, Masato Okada<sup>1</sup>

<sup>1</sup>Immuno-Rheumatology Center, St Luke’s International Hospital, <sup>2</sup>Division of Rheumatology, Juntendo Koshigaya Hospital, <sup>3</sup>Department of Nephrology and Rheumatology, Kochi University Hospital, <sup>4</sup>Department of Orthopedic Surgery, Osaka University

Conflict of interest: Yes

The terms spondyloarthritis, spondyloarthropathies, and seronegative spondyloarthropathy are used to refer to a family of diseases that share a group of clinical features. The preferred term for this family of arthritis is now “spondyloarthritis” (SpA). The group includes: ankylosing spondylitis, reactive arthritis (formerly Reiter’s syndrome), psoriatic arthritis, Juvenile SpA, enteropathic arthritis (spondylitis/arthritis associated with inflammatory bowel disease), and undifferentiated SpA. All display a variety of symptoms and signs, but they also share many features in common, including: inflammation of axial joints (especially the sacroiliac joints), asymmetric oligoarthritis (especially of the lower extremities), dactylitis (sausage digits), and enthesitis (inflammation at sites of ligamentous or tendon attachment to bone). Additional features include genital and skin lesions, eye and bowel inflammation, an association with preceding or ongoing infectious disorders, positive family history, elevated acute phase reactants, and a strong association with the human leukocyte antigen (HLA)-B27. The clinical manifestations, diagnosis, and classification of the SpA family of disorders in adults will be reviewed here with a focus on undifferentiated spondyloarthritis (USpA) and non-radiographic axial SpA (nr-axSpA). USpA and nr-axSpA are a frequent, severe and anti-TNF-responsive phenotypic subtype of SpA. In agreement with the new ASAS classification criteria for axial and peripheral SpA and emerging data on TNF blockade in non-radiographic axial SpA and peripheral uSpA, these data emphasize the need for early diagnosis and its differential diagnosis, and optimal treatment of not only AS and PsA but also other SpA subforms.

#### **S5-5**

##### **New bone formaion in ankylosing spndylitis**

Naoto Tamura

Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine, Tokyo, Japan

Conflict of interest: Yes

Ankylosing spondylitis (AS) is characterized by chronic inflammation of axial joints and subsequent irreversible new bone formation. Ossification is recognized by formation of syndesmophyte and ankylosis later that cause limited spinal mobility. Axial spondylitis initially occurs as enthesitis that recognized as osteitis of the adjacent bone by MRI. Then, squaring of the vertebral bodies, due to erosive changes caused by anterior and posterior spondylitis, is recognized in X-ray. Repair of the erosive lesions with fat infiltration is subsequently observed by MRI. It was reported that syndesmophytes appeared to be more frequent in post-inflammatory sites than ongoing inflammatory sites. NSAIDs are shown to inhibit new bone formation by possibly suppressing prostaglandin E2 that induces osteoblast differentiation. In contrast, TNF inhibitors were failed

to inhibit progression of bone disease at two years. However, recent studies have revealed that they may inhibit ossification when started earlier and used for longer duration. Bone morphologic proteins, Wnt/LRP pathways, and Wnt antagonists, such as Dkk-1 and sclerostin, are crucial molecules in subchondral bone formation, and they may be involved in new bone formation in AS. In addition, serum concentration of VEGF was shown to raise in AS and associated with subsequent new syndesmophyte formation. On the other hand, in membranous bone formation, mesenchymal cells directly differentiate into osteoblasts, and it may be also involved in the new bone formation in AS. Furthermore, it is recently reported that IL-23, whose gene is susceptible to AS, enhanced enthesitis through activation of enthesial resident T cells and also induced IL-22/STAT3-dependent bone formation in mouse, and serum IL-23 was elevated in AS patients indeed. IL-17 is induced by IL-23, and clinical trials of anti-IL-17 monoclonal antibody are now ongoing.

#### **S5-6**

##### **The latest therapeutic strategy in Spondyloarthritis**

Yoshinori Taniguchi<sup>1</sup>, Shigeto Kobayashi<sup>2</sup>, Yoshitaka Kumon<sup>4</sup>, Yoshio Terada<sup>1</sup>, Mitsumasa Kishimoto<sup>3</sup>

<sup>1</sup>Department of Nephrology and Rheumatology, Kochi University Hospital, <sup>2</sup>Division of Rheumatology, Juntendo Koshigaya Hospital, <sup>3</sup>Immuno-Rheumatology Center, St Luke’s International Hospital, <sup>4</sup>Division of Rheumatology, Chikamori Hospital

Conflict of interest: None

Ankylosing spondylitis (AS), a prototype of Spondyloarthritis (SpA), is a disorder causing chronic inflammation of axial joints, following new syndesmophyte (Synd) formation and irreversible bony ankylosis. Psoriatic arthritis (PsA) mainly affects peripheral joints. ASAS/EULAR currently suggest that SpA is classified as axial SpA (axSpA) including non-radiographic axial SpA (nr-axSpA) and peripheral SpA (pSpA) due to ASAS criteria. Recent reports have shown that trans-membrane typed TNF and IL-23/Th17 pathway played pivotal roles in SpA pathogenesis. Currently, NSAID and physical therapy are initiated for axSpA and then TNF inhibitors are considered according to ASAS/EULAR strategy. In ACR 2014, new treatment strategy for active or stable AS or nr-axSpA was suggested. The long-use outcome of TNF inhibitor for 8 years by European group showed that new Synd formation in TNF group progressed as same as control group for first 4 years, but new Synd formation was significantly prevented in TNF group for last 4 years. Moreover, it has recently reported that TNF inhibitors have been effect for early axSpA including nr-axSpA for 3 years. It is notable that erosions, sclerosis and fat metaplasia on imaging precede the subsequent development of Synd at the same site. Recent therapeutic reports showed that the combined lesions with inflammation and fat metaplasia developed new Synd despite of TNF inhibitors. Therefore, the establishment of early diagnosis and treatment for axSpA is desired. New potential agents other than TNF inhibitors, such as IL-17, PDE-4 and IL-12/23 inhibitor, are noted and we review these new therapeutic agents. On pSpA, we mainly describe about new treatments for PsA. TNF inhibitors and IL-12/23 inhibitor are applicable in Japan and PDE-4 inhibitor was approved in USA. IL-17 inhibitors go on clinical trial. Thus, the therapeutic strategy for axSpA and pSpA is established and goes on, and it’s time to establish the therapeutic strategy in Japan.

#### **S6-1**

##### **Involvement of T cell subsets in the pathogenesis of Sjögren’s syndrome**

Masafumi Moriyama, Sachiko Furukawa, Akihiko Tanaka, Takashi Maehara, Miho Ota, Masaki Yamauchi, Jun-Nosuke Hayashida, Seiji Nakamura

Section of Oral and Maxillofacial Oncology, Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University

Conflict of interest: None

**[Objectives]** Sjögren’s syndrome (SS) is an autoimmune disease characterized by lymphocytic infiltration of the salivary and lacrimal glands with the concomitant destruction of glandular tissue. Previous

studies have shown that CD4-positive T helper (Th) cells predominantly infiltrate salivary glands at an early stage of SS, and may be critical in the induction and/or maintenance of the disease. In order to determine the involvement of Th subsets in the initiation and progression of SS, we examined the salivary glands and saliva from SS patients to identify the expression patterns of Th-related molecules and their association with the ectopic germinal center (eGC) formation. **[Methods]** The expression of Th-related molecules such as cytokines, chemokines/chemokine receptors, and transcription factor in the labial salivary glands (LSGs) from SS patients and healthy controls was examined using real-time PCR and immunostaining. Additionally, infiltrating lymphocytes without germinal centre (GC (-)) and with GC (GC (+)) in the LSGs specimens from eight SS patients were extracted selectively by laser capture microdissection. The mRNA expression of these molecules was compared between the two sample groups of GC (-) and GC (+) by real-time PCR. **[Results]** In LSGs from patients with SS, mRNA expression of Th1-, Th2-, Th17-, Tfh-related molecules was higher than those in controls. Th2 and Tfh was associated closely with strong lymphocytic infiltration. In the selectively extracted lesions of LSGs, Th1 and Th17-related molecules were detected strongly in the GC (-), while Th2 and Tfh-related molecules were detected in the GC (+). **[Conclusion]** These results suggest that SS might be initiated by Th1 and Th17 cells, and then progressed by Th2 and Tfh cells via eGC formation. In this presentation, we review the relationship between the pathogenesis and Th subsets based on our recent findings.

## S6-2

### A challenge to a disease modifying therapy for Sjögren's syndrome by focusing on monocytes and B cells

Keiko Yoshimoto, Eriko Ishioka, Ayumi Nishikawa, Katsuya Suzuki, Tsutomu Takeuchi

Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine

Conflict of interest: None

Sjögren's syndrome (SS) is an idiopathic autoimmune disease whose major clinical manifestations are dry mouth and dry eyes. A focal lymphocytic infiltrate of the exocrine glands is responsible for lesion formation and the subsequent dysfunction of the glands. It is likely that inflammatory responses associated with SS are caused by autoantibodies produced by abnormally activated B cells. Therefore, suppression of the autoantibody production may provide disease modifying therapy for SS. Accumulating evidence has suggested that BAFF (B cell activating factor belonging to the TNF family) is involved in the pathogenesis of SS. We have focused on monocytes (CD14<sup>+</sup> cells) and B cells, and found their functional abnormalities in SS. First, SS monocytes showed an abnormal response to BAFF stimulation which resulted in increased production of IL-6. We revealed that the abnormality was, in part, attributed to the elevated expression of a BAFF receptor, BR3. Second, a positive and significant correlation was observed between the BR3<sup>+</sup>/CD14<sup>+</sup> ratio of SS monocytes and IL-6 production in vitro by the cells. Notably, the ratio was also positively and significantly correlated with serum IgG level of SS patients. Third, BAFF-stimulated SS monocytes enhanced IgG production by SS B cells through an IL-6 signaling pathway. Fourth, the proportion of CD38<sup>+</sup> subset among peripheral B cells was increased in SS, and that IgG production by the subset was abnormally elevated upon stimulation of BCR. These data imply that abnormalities of both monocytes and B cells are involved in the pathogenesis of SS. We postulate that these abnormalities result in hypergammaglobulinemia, which is often concurrent with SS. Elucidation of the molecular mechanisms of these abnormalities may lead to new therapies for SS. We believe the BAFF-signaling pathway provides prospective therapeutic targets for drug discovery to treat SS.

## S6-3

### Sjögren's syndrome update – from the view point of apoptosis

Hideki Nakamura, Yoshiro Horai, Atsushi Kawakami

Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences

Conflict of interest: None

Apoptosis is included as one of etiological mechanisms of Sjögren's syndrome (SS). Relevant proteins contain pro- and anti-apoptotic molecules. A typical model is a Fas/Fas ligand system. Though Fas was observed in acinar epithelial cells or luminal side of ducts in labial salivary glands (LSGs), Fas ligand was observed in infiltrating mononuclear cells (MNCs) or ductal lumen. In saliva, soluble Fas ligand increased and was significantly high in advanced group. Though peripheral CD3<sup>+</sup> T cells had neither CD40 nor CD40 ligand, many MNCs expressed CD40 or CD40 ligand. Since CD40-positive cells expressed Bcl-2, it was considered B cells activated by stimulation of CD40-CD40 ligand escaped from apoptosis. Additionally, CD40-positive MNCs expressed c-Jun N-terminal kinase and p38, suggesting relevancy with prolongation of sialadenitis. Meanwhile, phosphorylated-Akt (p-Akt) and nuclear expression of NF- $\kappa$ B was observed in LSGs of SS. Additionally, anti-Fas antibody combined with LY294002 or Bay 11-7082 induced significant apoptosis. Epidermal growth factor (EGF) that is secreted from salivary gland dose-dependently inhibited apoptosis. Though TNF- $\alpha$  induced no apoptosis in cultured SGEs, tumor necrosis factor-related apoptosis ligand induced intensive apoptosis within 3hrs. As this mode of action, activation of mitochondrial pathway was involved. Meanwhile, it was shown that toll-like receptor3 (TLR3) induced apoptosis of SGEs with activation of p-Akt or MAP kinases by stimulation with TLR3 ligand, poly I: C. Besides, when expression of downstream signal of TLR3 was observed, weak expression of RIPK3 and no expression of phosphorylated-FADD (p-FADD) and cleaved-caspases were found in LSGs. However, these molecules were activated in poly I: C-stimulated SGEs. Though stimulation of SGEs with EGF activated HO-2 or HSP-27 that are survival factors, EGF dose-dependently inhibited p-FADD, suggesting that these factors controlled cell death at downstream of TLR3 in vivo.

## S6-4

### Cytokine profiles of saliva in patients with Sjögren's syndrome: association between salivary EGF levels and the severity of intraoral manifestations

Naoto Azuma<sup>1</sup>, Yoshinori Katada<sup>2</sup>, Sachie Kitano<sup>1</sup>, Aki Nishioka<sup>1</sup>, Masahiro Sekiguchi<sup>1</sup>, Masayasu Kitano<sup>1</sup>, Kiyoshi Matsui<sup>1</sup>, Hajime Sano<sup>1</sup>  
<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan, <sup>2</sup>Department of Internal Medicine, Sakai City Hospital, Sakai, Japan

Conflict of interest: None

**Background:** In Sjögren's syndrome (SS), intraoral manifestations are believed to be caused by a decreased clearance in the oral cavity due to hyposalivation. Because saliva has several physiological effects on the oral environment, however, qualitative changes in sialochemistry should be considered. Salivary epidermal growth factor (EGF) is considered to be an important cytoprotective factor and it contributes to wound healing in the oral cavity. **Objectives:** We examined changes in salivary EGF levels and assessed the association between salivary EGF levels and the severity of intraoral manifestations in SS patients. **Methods:** (1) Forty SS patients and 23 controls were enrolled. Salivary EGF levels were measured using an ELISA kit, and intraoral manifestations were evaluated using a short version of the Oral Health Impact Profile (OHIP-14). The associations among salivary flow rate, EGF levels, and the severity of intraoral manifestations were analyzed. (2) 23 SS patients and 14 controls, followed up for three years, were re-examined. **Results:** (1) The total salivary EGF output was decreased in the SS group compared with the non-SS group (9237.6 vs 13296.9 pg/10 min, p=0.033). In the SS group, EGF output and salivary flow rate showed a strong positive correlation ( $r_s=0.824$ , p=0.0005), while EGF output and disease duration showed a negative correlation ( $r_s=-0.484$ , p=0.008). Further, EGF output was significantly correlated with the OHIP-14 score ( $r_s=-0.721$ , p=0.012). (2) In SS, the OHIP-14 score was significantly increased and total EGF output was significantly decreased after three years follow-up (10158.4 vs 8352.8 pg/10 min, p=0.032). EGF output change was significantly correlated with the OHIP-14 score change in patients with poor oral QOL ( $r_s=-0.847$ , p=0.008). **Conclusions:** The salivary EGF levels are decreased with time in SS, and this deterioration in saliva quality causes refractory intraoral manifestations. Our findings provide new therapeutic targets for SS.

## S6-5

### Clinical application of ESSPRI and ESSDAI, disease activity indices for Sjögren's syndrome

Susumu Nishiyama

Rheumatic Disease Center, Kurashiki Medical Center

Conflict of interest: None

Evidence-based therapy for Sjögren's syndrome (SS) is largely limited to treatments that improve sicca features. A variety of ad hoc outcome measures mainly based on glandular features or patient symptoms had been used; however, international standard activity indices are needed to assess the effectiveness of new targeted therapies, such as B-cell targeted therapies for severe systemic features. Thus, EULAR SS task force has developed two disease activity indices: one is EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), and the other is EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI). Validation of two indices revealed that ESSPRI and ESSDAI correlated with patient and physical global assessment, respectively, and both indices were reliable. ESSPRI is the average score of dryness, fatigue, and pain, and it ranges from 0 to 10. Unlike patient global assessment its distribution is nearly normal, so that it is easy to handle statistically. ESSDAI has 12 organ-specific domains which were ranked by four levels of activity: no (0), low (1), moderate (2), and high (3). ESSDAI is the sum of the products of weight and activity in each domain. The maximum theoretical ESSDAI score is 123; however, the highest score in clinical study was around 40. Since ESSPRI and ESSDAI do not correlate to each other, simultaneous use of both indices is recommended. Two valid indices are now using for assessing disease activity and response for treatment; besides, you can apply them to inclusion criteria in clinical trials or therapeutic guidelines in daily practice. Some investigators try to forecast developing malignant lymphoma by scoring ESSDAI. You can also examine a specific symptom or domain by analyzing each component of ESSPRI and ESSDAI. Applying these international standard indices permit us to compare the obtained data easily and to share them globally, that would facilitate the establishment of a therapeutic guideline for SS.

## S6-6

### New therapeutic strategy for Sjögren's syndrome targeted on T cells

Hirotoshi Tsuboi<sup>1</sup>, Isao Matsumoto<sup>1</sup>, Shinya Hagiwara<sup>1</sup>, Tomoya Hirota<sup>1</sup>, Hiroyuki Takahashi<sup>1</sup>, Hiroshi Ebe<sup>1</sup>, Masahiro Yokosawa<sup>1</sup>, Shintaro Hirata<sup>2</sup>, Yoshiro Horai<sup>3</sup>, Hiromitsu Asashima<sup>1</sup>, Naoto Umeda<sup>1</sup>, Yuya Kondo<sup>1</sup>, Hiroshi Ogishima<sup>1</sup>, Takeshi Suzuki<sup>1</sup>, Kazuyoshi Saito<sup>2</sup>, Yoshiya Tanaka<sup>2</sup>, Hideki Nakamura<sup>3</sup>, Atsushi Kawakami<sup>3</sup>, Takayuki Sumida<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan, <sup>2</sup>The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Fukuoka, Japan, <sup>3</sup>Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Conflict of interest: Yes

<Objective> To clarify the efficacy and safety of abatacept for secondary Sjögren's syndrome (SS) associated with rheumatoid arthritis (RA). <Methods> We designed open-labeled, prospective, observational, and multicenter study (ROSE trial; Rheumatoid Arthritis with Orencia Trial Toward Sjögren's syndrome Endocrinopathy) for secondary SS (diagnosed by 1999 revised Japanese diagnostic criteria) associated with RA (diagnosed by 1987 ACR or 2010 ACR/EULAR criteria), who were over 20 years old and consented to this study. 1) Primary endpoint was frequency of Simplified Disease Activity Index (SDAI) remission at 52 weeks after initiation of abatacept. 2) Secondary endpoints included Saxson's test and Schirmer's test. 3) Adverse events during observational periods were also analyzed. <Results> Thirty two patients (all females) had been enrolled in this study. Interim analysis for 24 weeks included assessment for effectiveness in 31 patients and safety in 32 patients. 1) The mean SDAI significantly decreased from 19.8±11.0 (0 week, baseline) to 9.9±9.9 (24 weeks) ( $P<0.05$ ) after initiation of abatacept. Patients with clinical remission by SDAI increased from 0 patient (0 week) to 8 patients (25.8%) (24 weeks). 2) Saliva volume by Saxson's test increased slightly from 2232±1908 (0 week) to 2424±2004 (24 weeks) mg/2 min in 29 patients. In 11 patients with Greenspan grading 1 and 2 of labial sali-

vary glands biopsy, saliva volume significantly increased from 2945±2090 (0 week) to 3419±2121 (24 weeks) mg/2 min ( $P<0.05$ ). Tear volume by Schirmer's test significantly increased from 3.6±4.6 (0 week) to 5.5±7.1 (24 weeks) mm/5 min ( $P<0.05$ ). 3) Five adverse events occurred in five patients out of 32 patients (15.6%), and three of them were infections. Although abatacept was interrupted in 3 patients, it has been restarted after recovery of the adverse events. <Conclusion> These results indicated that abatacept might be effective for both SS and RA involvements in secondary SS with RA.

## S7-1

### New strategy

Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational & Environmental Health, Japan

Conflict of interest: Yes

Rheumatoid arthritis (RA) is a systemic autoimmune disease with synovitis and joint destruction that causes significant morbidity and mortality. However, synthetic DMARDs such as methotrexate (MTX) and biological DMARDs targeting TNF has revolutionized treatment of RA and clinical remission is realistic goals achieved by a large proportion of RA patients. Furthermore, the maintenance of remission has produced significant improvements in radiographic and function outcomes. Although many pivotal targeted therapies are currently under the development, the majority of them have failed and it is hard to overcome the present synthetic DMARDs. On the other hand, the construction of new therapeutic strategies has been emerging. The post-marketing surveillance of biological DMARDs has provided enormous information and has clarified safety profile of the drugs and risk factors affecting severe adverse events and severe infectious events, which has brought valuable information, how to make prophylaxis, how to manage these events and how to safely treat patients. We also need to create the therapeutic strategies for the long-term maintenance after obtaining remission in order to keep structural, functional and comprehensive remission. However, there are concerns about long-term safety by using synthetic DMARDs and economic burden associated with biological DMARDs. Thus, de-escalation of synthetic and/or biological DMARDs appears to attract attention to strategically treat RA. Recent studies indicate that approximately half of early RA patients could discontinue biological DMARDs targeting TNF after obtaining remission. However, fewer patients successfully discontinued biological DMARDs in established RA, but "deep remission" at the discontinuation is a key factor to keep the treatment holiday of biological DMARDs. Since we have obtained strong weapons to treat RA, a new strategy rather than a new target should be required for the advanced therapy of RA.

## S7-2

### New targets in RA treatment

Tsutomu Takeuchi

Division of Rheumatology, Department of Internal Medicine, Keio University, School of Medicine, Tokyo, Japan

Conflict of interest: Yes

The targeted therapy in rheumatoid arthritis (RA) is now widely accepted in clinical practice. Targeted synthetic and biological DMARDs provide powerful means to control disease activity, making clinical remission as a realistic treatment target in addition to conventional synthetic DMARDs such as methotrexate. However, it is not so easy really to achieve clinical remission within 6 months after starting a given drug in clinical practice and it is even true after adjusting and changing the drugs several times from the initial DMARDs. The treatment strategy for the patients having comorbidities and or experienced with the side effects of DMARDs should also be considered. In order to solve these difficulties, one direction may be to identify new targets with distinct efficacy and safety profiles over the existing known targets. In this symposium, I would like to focus on the new targets, on which the biological agents had been tested in early/late phase II trials with the positive results. For example, fully human monoclonal antibody against GM-CSF receptor, mavrilimumab, exhibited the excellent efficacy and acceptable tolerability in EARTH trial. By reviewing the result, the role of the targets, GM-

CSF receptor and the ligands GM-CSF in pathogenesis of RA or inflammation are discussed. In addition, I shed light on another new target, RANKL. Fully monoclonal antibody against RANKL, denosumab, is already approved for osteoporosis, but the indication for RA has not yet been obtained globally. Japanese clinical trial designated as DRIVE for the patients with RA has shown the positive results. By reviewing the core trial data for DRIVE and the updated new data, the significance and uniqueness of the target is discussed. Given these new information, I would like to add comments on the impacts of the new targets on the current treatment strategy and future perspective for RA therapy.

### S7-3

#### New Kinase Inhibitors

Koichi Amano

Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University

Conflict of interest: Yes

In the 2014 ACR annual meeting, tofacitinib has been placed as a second-line DMARD as well as biologic agents for the treatment of active established RA patients who have inadequately responded to the first DMARD (mainly MTX). Now, various kinds of JAK inhibitors other than tofacitinib are being developed. In this symposium, I'll show some promising data of new small molecular agents. Baricitinib is a selective JAK inhibitor. Phase 2b trial data of baricitinib has been published. Significantly more patients (76%) in the combined baricitinib 4 mg and 8 mg groups compared with placebo (41%) achieved an ACR 20 response at week 12 ( $p < 0.001$ ). Though 3 patients of baricitinib groups had serious infections, baricitinib was well tolerated without any unexpected safety issues during 24-week observation period. In addition, on Dec 9<sup>th</sup> in 2014, Eli Lilly co. and Incyte announced that the phase 3 RA-BEACON study which was done for RA patients who had failed one or more TNF inhibitors met the primary endpoint of improved ACR 20 response at week 12. Then I'd like to introduce the newest promising data of other JAK inhibitors; two selective JAK1 inhibitors GLPG-0634 (filgotinib) and INCB-039110, a selective JAK3 inhibitor VX-509 (decernotinib), and a pan-JAK inhibitor ASP015K (peficitinib) which inhibits all 4 JAKs. There are some candidate target kinases other than JAK such as MAPK, PI3K and Syk. However, a p38-MAPK inhibitor pamapimod and Syk inhibitor fostamatinib could not show better results as compared with MTX. As tofacitinib has been shown to be more effective than MTX (ORAL Start study), this kind of drugs could take over MTX as an anchor drug for RA in the future. Only after a decade from the introduction of biologics, new paradigm shift could occur by small molecule agents such as JAK inhibitors in the field of RA therapy.

### S7-4

#### View of Innovative Therapeutic Antibodies

Masayuki Tsuchiya

Chugai Pharmaceutical Co. Ltd.

Conflict of interest: None

24 years has passed since we had collaboration with MRC on ACTEMRA which is Humanization of anti-IL-6 receptor antibody. At the time we started, there were a few companies interested in Therapeutic Antibodies (Mabs), however, expectation for Mabs became larger followed approval of Herceptin, Rituxan, Remicade, Avatin and Humira, so called "Blockbuster" later. In such these situation, ACTEMRA had been on with a global development plan as the first Japan-origin Mabs and approved more than 100 countries in the world. 30-40 products were expected to appear in the market since then, and, now 36 Mabs have been approved and other than that on being applied, clinical development and the next generation of Mabs with innovative technologies, so it gains momentum much more than we expected. The other, in the future, since the first generation of Mabs will sure to be faced on the patent-expiry, the development of Bio-similar/Bio-better becomes focused on. In addition, the technology innovation on Mabs development is remarkable, and many improvements, such as, from Chimera to Humanized, to Human, to reduce immunogenicity, to strengthen the effect by modifying both variable and constant regions, and more optimization of physical properties on

stability and pharmacokinetics, and to reduce the cost of industrial production, were being dramatically solved. Especially, the technology innovation is into practice on the new concept of the MOA of Mabs and on the realization of the added product value. Thus, the search of innovative Mabs on "First in Class" and the competition of the development being affected by the differentiation on "Best in Class" are heated-up more and more. In this session, I would like to introduce the possibility of the technology innovation on Mabs development next future step.

### S7-5

#### Design of antibody drug using supercomputer

Tatsuhiko Kodama, Hideaki Fujitani

Research Center for Advanced Science and Technology

Conflict of interest: Yes

The prediction of protein-protein interaction using molecular dynamics simulation is one of the most rapidly growing areas in drug design. Advanced cancer with relapse and metastases are the leading causes of death in Japan. Besides the physical suffering caused by cancer, multiple organ failures, and the side effects of surgery, chemotherapy, or radiation therapy, patients must also face a significant financial burden associated with cancer treatment. MDADD (Molecular Dynamics for Antibody Drug Development/Antibody-structure-based design Projects) is a funded from the Japanese Government as one of 30 FIRST programs. Through the screening of the monoclonal antibody library, a lead monoclonal antibody for cancer will be selected using PET imaging and cancer-bearing animals. Based on X-ray crystal structure and a thermodynamic analysis of antigen-antibody complex, a construct of a single-chain variable fragment (scFv) fused with "humanized" streptavidin (SA) with reduced antigenicity, will be designed using molecular dynamics simulation. Artificially designed Biotin labeled with  $\gamma$ -emitting radionuclides will be used for PET diagnostics and biotin labeled with  $\beta$ -emitting radionuclides will be used for treatment. With this approach, we will develop pre-targeting antibody drugs that are safe for humans. In this meeting we will report a molecular dynamics design of anti-colon cancer antibody against epiregulin, a cell surface maker for colon cancer stem cells.

### S8-1

#### Keynote lecture: Clinicopathological aspects of lupus nephritis in Japanese

Hitoshi Yokoyama

Division of Nephrology, Kanazawa Medical University School of Medicine, Uchinada, Japan

Conflict of interest: Yes

Lupus nephritis comprises a various pathological spectrum of glomerular, vascular, and tubulo-interstitial lesions, which has significant racial variation in severity and manifestations. About 21-65% of Asian patients with lupus are reported to have abnormal urine test results in their early disease courses, and up to 40-82% of adults may go on to develop overt renal abnormalities. The current classification (ISN/RPS 2003) has been improved successfully for the categorization of lupus glomerulonephritis (LGN). On the basis of this classification, 480 Japanese cases including 198 cases of the Japan renal biopsy registry (J-RBR) revealed the following distribution: class I 3.1%, class II 16.0%, class III 12.9%, class IV-S 10.6%, class IV-G 40.6%, class V 15.6%, and class VI 1.0%. IV-G with active and chronicity tended to have a worse renal outcome. The frequency of nephrotic syndrome complication in Japanese biopsy-proven lupus nephritis was 83 out of 183 cases (45.4%) in 3 reports from Gumma, Okayama and Kanazawa University. Nephrotic syndrome was a more frequent complication in class IV-S (50.0%), class IV-G (71.8%), and class V (56.0%) with poor renal and actuarial outcomes. However, this classification did not include recently recognized glomerular lesions such as lupus podocytopathy and collapsing glomerulopathy, tubulo-interstitial, and vascular lesions. New classification of lupus nephritis including recent reports is expected to do the more accurate clinicopathological diagnosis. With regard to therapy, treatment options including glucocorticoids alone or combined with antimetabolites (AZP, MZB, MMF), calcineurin inhibitors (CsA, Tac), or alkylating agents (IVCY) improved the outcomes of LGN. However, there is no high-grade clinical

evidence from Japan. Further studies are needed to resolve the clinicopathological problems of LGN, especially IV-S, IV-G, and pure MLN in Japanese.

## S8-2

### SLE-associated thrombotic microangiopathy

Hiroaki Niiro

Kyushu University Hospital, Clinical Education Center

Conflict of interest: None

Thrombotic microangiopathy (TMA) is generally characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia and organ ischemia. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are the two principal diseases associated with TMA. The etiology of TMA includes congenital disorders, infection, malignancy, transplantation, pregnancy, adverse effects of drugs, and connective tissue diseases. Our understanding of the pathogenesis of TMA was greatly facilitated by the discovery of the von Willebrand factor (VWF)-cleaving enzyme, ADAMTS13. A reduction in ADAMTS13 activity is closely associated with impaired degradation of VWF multimers, culminating in the intravascular aggregation of platelets followed by organ damage. This typical form of TTP is caused by mutations of the ADAMTS13 gene and the presence of anti-ADAMTS13 antibody. However, in TTP associated with SLE, a marked reduction in ADAMTS13 activity due to an anti-ADAMTS13 antibody is relatively rare, while slightly decreased or normal ADAMTS13 activity is more common. This atypical form of TTP might be due to the activation and damage of endothelial cells, complement activation and increased production or cleavage-resistance of VWF. Given that TMA is relatively rare but a refractory disorder with poor prognosis, early diagnosis and treatment are essential for favorable outcome. Although therapeutic plasma exchange (PE) is an effective treatment for the typical form of TTP, non-ADAMTS13 mediated atypical form of TTP does not respond well to PE and requires additional immunosuppressive therapies, albeit still with poor prognosis. Further understanding of its pathogenesis might pave a new avenue for the treatment of TMA associated with SLE.

## S8-3

### Pathogenesis of recalcitrant neuropsychiatric systemic lupus erythematosus

Shunsei Hirohata

Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan

Conflict of interest: None

Neuropsychiatric manifestations in systemic lupus erythematosus (SLE) are difficult complication that may cause substantial impairment of quality of life as well as disability. Among a variety of neuropsychiatric manifestations in SLE, acute confusional state (ACS) in diffuse psychiatric/neuropsychological syndromes (diffuse NP-SLE) is the most serious one. Recent studies have demonstrated that the presence of neuron-reactive autoantibodies in cerebrospinal fluid (CSF) plays a pivotal role in the pathogenesis in diffuse NPSLE. Thus, anti-NMDA receptor NR2 (anti-NR2) and anti-Sm antibodies, which react with neuronal cells, are associated with diffuse NP-SLE, most notably in ACS. However, the precise mechanism of elevation of CSF anti-NR2 and anti-Sm remained uncertain. Overall, there are 2 mechanisms for the elevation of CSF IgG, including transudation through the damaged blood-brain barrier and intrathecal synthesis. Previous studies have revealed that intrathecal synthesis of immunoglobulins was elevated in NP-SLE, whereas the damage of blood-brain barrier was modest. We have recently revealed that CSF anti-NR2 and anti-Sm levels and Q albumin were significantly higher in acute confusional state (ACS) than in non-ACS diffuse NPSLE (anxiety disorder, cognitive dysfunction, mood disorder and psychosis) or in focal NPSLE, whereas there was no significant difference in CSF anti-NR2 or anti-Sm index and serum anti-NR2 and anti-Sm levels among the 3 groups. CSF anti-NR2 levels were significantly correlated with CSF anti-Sm levels in NP SLE, whereas there was no significant correlation between serum anti-NR2 and serum anti-Sm. Both CSF anti-NR2 and anti-Sm levels were significantly correlated with Q albumin. These results

demonstrate that the severity of blood-brain barrier damages plays a crucial role in the development of ACS, the most recalcitrant form of diffuse NPSLE.

## S8-4

### Thrombosis and vascular damages in systemic lupus erythematosus

Shinsuke Yasuda

Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine

Conflict of interest: Yes

Patients with systemic lupus erythematosus (SLE) are prone to vascular damage such as thromboembolism associated with the presence of antiphospholipid antibodies, thrombotic thrombocytopenic purpura, atypical HUS, vasculitis and pulmonary artery hypertension according to the disease activities and premature atherosclerosis as a result of corticosteroid treatment or lupus itself. The most frequent vascular lesion is thromboses associated with aPLs. Such thromboembolisms are represented by ischemic cerebral infarction/thrombosis or transient ischemic attack in terms of arterial lesions, whereas represented by deep vein thrombosis and accompanying pulmonary embolism in terms of venous lesions. According to our single center observation, incidence of arterial thrombosis represented by cerebral infarction was higher when compared with that found in Caucasian populations. aPLs target  $\beta$ 2-glycoprotein I, prothrombin and other phospholipid binding proteins. Because of the multiplicity of self-antigen, measurement of aPLs require more than two assay systems: coagulation assays such as lupus anticoagulant and immunological assays such as anti- $\beta$ 2-glycoprotein I antibody or phosphatidylserine dependent prothrombin antibody. We defined antiphospholipid score (aPL-S) by testing multiple aPLs and demonstrated its efficacy in predicting the recurrence of thrombosis. Secondary prophylaxis of thrombosis is a primary objective of the treatment, but the current treatment strategies including anticoagulation and/or anti-platelet reagents are not sufficient to sufficient to prevent the recurrence and comprise risks for unwanted bleedings. Recently, effects of statins in the suppression of recurrent thrombosis are suggested. We also confirmed the effectiveness of statin in the second prophylaxis for thromboembolism in our patient cohort. More anecdotally, hydroxychloroquine as well as rituximab might be useful for the treatment for the APS, although further investigation would be required.

## S8-5

### Diffuse alveolar hemorrhage associated with SLE

Naoichiro Yukawa

Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Conflict of interest: None

The survival of patients with systemic lupus erythematosus (SLE) has improved during last several decades, and the adequate use of corticosteroids (CS), the new advances in the second line therapies including immunosuppressive agents, plasmapheresis (PP), and hemodialysis, and the appropriate control of infectious complications are the major factors. On the other hands, diffuse alveolar hemorrhage (DAH) is a rare but life-threatening complication of SLE. The frequency of DAH associated with SLE (SLE-DAH) has been reported 1.6% of SLE cohort or 3.7% of hospital admissions due to SLE. When the disease occurs once, SLE-DAH is often fatal with reported mortality rates of 53% to 92%. Because of the extremely rare frequency and the high mortality rates, none of the recommended therapies of SLE-DAH have been assessed in a controlled manner. Therefore, we have to review the details of literatures of small pilot studies and case reports of SLE-DAH to treat this life-threatening complication. DAH is bleeding into the alveolar spaces, due to disruption of the alveolar-capillary basement membrane. This is caused by injury or inflammation of the arterioles, venules, or alveolar septal (alveolar wall or interstitial) capillaries. The onset of DAH is often abrupt or of short duration, and cough, hemoptysis, fever, and dyspnea are common initial symptoms. But the fact that hemoptysis may be absent at presentation should be noted. The diagnosis of DAH is established by new alveolar infiltrates, progressive anemia, and the finding of increasingly hemor-

rhagic fluid on sequential bronchoalveolar lavage. Aggressive management with high dose CS including methylprednisolone pulse therapy, cyclophosphamide (CY), and PP should be started immediately if pDAH is suspected. In this symposium, we present the course, treatments, and prognosis of patients with SLE-DAH who were treated in our department. We also show the results of the literature review of the previous reports of SLE-DAH.

## S8-6

### Refractory hematologic disorders in systemic lupus erythematosus: immune thrombocytopenia and hemophagocytic syndrome

Masataka Kuwana

Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine

Conflict of interest: Yes

Hematologic disorders, including decreased counts in lymphocytes and platelets, are common laboratory abnormalities in patients with active systemic lupus erythematosus (SLE), but they are often mild, and do not require treatment or represent recovery after treatment for other manifestations of SLE. However, immune thrombocytopenia (ITP) and hemophagocytic syndrome (HS) can be serious and require intensive treatment. ITP is mediated by IgG autoantibodies to platelet surface glycoproteins, which lead to enhanced platelet clearance in periphery and suppression of platelet production. Corticosteroids are often effective, but recurrence after corticosteroid tapering or sustained thrombocytopenia without additional disease activity requires treatment with immunosuppressants. Splenectomy is the most effective option, but eradication of *Helicobacter pylori* is ineffective. Rituximab now attracts attention as an alternative second-line treatment. Thrombopoietin receptor agonists that stimulate platelet production are a new class of drugs. Several clinical trials in patients with primary ITP have demonstrated high efficacy and continuance rate, but experiences in patients with SLE-ITP are currently scanty. On the other hand, HS is referred to as macrophage activation syndrome, but the primary mediator is shown to be different between underlying conditions: TNF alpha in SLE versus IL-6 in Still's disease. More than 70% of patients with SLE-HS respond to corticosteroids, but refractory cases require additional treatment with cyclosporine, intravenous cyclophosphamide, or intravenous immunoglobulin. In addition, recent case series reported anti-TNF biologics and rituximab as potential treatment options for refractory cases. There are many treatment options for refractory ITP and HS, but information on which treatment should be chosen as the second-line treatment is lacking. Personalized treatment approach may be necessary to overcome these serious complications.

## S9-1

### Genome-wide association studies in Behçet's disease

Yohei Kirino

Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine

Conflict of interest: None

Behçet's disease is common in Asia, regions along the ancient Silk Route. Although its etiology is still uncertain, evidence suggests both environmental and genetic factors. Well-established genetic factor of Behçet's disease is HLA-B\*51, but other genetic factors convincingly associated with the disease were not discovered for a long time. Recently, we performed genome-wide association studies involving Japanese and Turkish patients, and identified several susceptibility loci including *IL10*, *IL23R*, *ERAP1*, *STAT4* that have function in both innate and acquired immunity. In addition, we found evidence of genetic interaction between HLA-B\*51 and *ERAP1* disease-associated variants. *ERAP1* is an aminopeptidase expressed in endoplasmic reticulum that trims peptides into optimal size and loads peptides onto HLA-Class I antigen binding groove. The result strongly indicates that peptide handling mechanisms is critical for the pathogenesis of Behçet's disease. Genetics interaction between *HLA-Class I* and *ERAP1* variants, and association with *IL23R* are also reported in ankylosing spondylitis and psoriasis. These results implicate common pathogenic pathways among seronegative *HLA-Class I*-associated diseases. We also performed imputation and fine-mapping of HLA

region, which revealed novel disease-associated alleles such as HLA-A\*03, B\*15, and A\*26. HLA Class I amino-acid association showed that residues associated with Behçet's disease are mostly found in critical positions in peptide binding and MHC-I–killer immunoglobulin-like receptor interactions. I will introduce latest genetics findings in Behçet's disease including targeted-resequencing and Immunochip analysis.

## S9-2

### Genomic studies of Idiopathic osteonecrosis of the femoral head

Shiro Ikegawa

Laboratory for Bone and Joint Diseases, RIKEN Center for Integrative Medical Sciences

Conflict of interest: None

Idiopathic osteonecrosis of the femoral head (ION) is an incurable disease that new cases will occur in about 3,000 people every year in Japan. From epidemiological studies, ION is subdivided into: 1) 'steroidal' that occurs after a large amount of steroid administration for the treatment of collagen disease such as SLE and renal transplantation; 2) 'alcoholic' that is found in patients with a large amount of drinking history; 3) the narrow sense of ION (other than the former two). However, the cause is unknown, and there is no effective prevention method or definitive treatment. The purpose of this study is to clarify the genetic factors of ION through large-scale genome analysis, including whole exome sequencing and whole-genome association study (GWAS). All the main facilities doing a treatment for ION are participating in the Scientific Research group of ION funded by Research on rare and intractable diseases, Health and Labour Sciences Research Grants. In cooperation with this group, we are performing a comprehensive genome analysis of ION under All Japan regime. Specifically, we are performing the following research. 1) Candidate gene analysis of ION-like single gene diseases (skeletal dysplasia) 2) Exome analysis of the narrow sense of ION 3) GWASs for steroidal, alcoholic and narrow sense of ION. Through these, we would identify the causative gene (disease gene, disease susceptibility gene) to establish precise diagnostic criteria of ION and elucidate its molecular pathogenesis, leading to the innovative treatment.

## S9-3

### Genetic risks for radiographic progression in RA patients

Katsunori Ikari

Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: Yes

Rheumatoid arthritis (RA) is a common autoimmune disease characterized by the chronic synovitis and the localized destruction of cartilage and bone resulting in deteriorated physical function and reduced quality of life. Since RA is a complex disease influenced by both genetic and environmental factors, susceptibility genes to the disease have been widely investigated and identified, especially in the era of genome-wide association studies (GWAS) and GWAS meta-analyses. Recently, a large-scaled GWAS meta-analysis was conducted using >100,000 samples. As a result, 101 RA susceptibility loci were identified including 42 novel loci. However, it is not clear whether these loci have significant impact on joint destruction or not. We investigated independent genetic risk factors for radiographic progression in the first five years from onset of RA using GWAS.

## S9-4

### From genome-wide analysis to genome-based drug discovery

Yukinori Okada<sup>1,2</sup>

<sup>1</sup>Department of Human Genetics and Disease Diversity, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, <sup>2</sup>Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan

Conflict of interest: None

A major challenge in human genetics is to devise a systematic strategy to integrate disease-associated genetic variants with diverse genomic

and biological datasets to provide insight into disease pathogenesis and guide drug discovery. We have demonstrated one such strategy for rheumatoid arthritis (RA), a common autoimmune disease destructing joints. Through a trans-ethnic genome-wide association study (GWAS) in a total of >100,000 subjects from multiple populations, which entirely evaluates diseases risk of the whole genome genetic variants, we discovered 42 novel RA genetic risk loci, bringing the total to 101. We constructed an in silico bioinformatics pipeline to systematically integrate the identified RA risk genetic loci with a variety of biological databases including immune-cell specific gene expressions, hematological cancer mutation genes, primary immunodeficiency genes, and epigenetic histone motifs, which provided novel biological insights of RA pathogenicity. The HLA imputation method identified HLA gene polymorphisms as disease biomarkers, and polygenic analysis using whole-genome SNPs provided novel insights into the epidemiology of diseases. We also demonstrate that RA risk genetic loci are enriched for genes that are the target of approved therapies currently used for RA treatment. This observation suggests that drugs approved for other disease indications may be repurposed for the treatment of RA (e.g., CDK4/CDK6 inhibitors currently indicated for cancers). Together, our study provides empirical evidence that the human genetics can provide important information for human diseases, including novel therapeutic targets and drug discovery.

### S9-5

#### Association of Human Leukocyte Antigen with Susceptibility for Rheumatic Diseases or Response to Disease Modifying Anti-Rheumatic Drugs

Hiroshi Furukawa, Shigeto Tohma

Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara National Hospital, Sagamihara, Japan

Conflict of interest: Yes

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that affects about 1% of population and is associated with the development of extra-articular manifestations. RA pathogenesis is multifactorial and the disease susceptibility is associated with genetic and environmental factors. Human Leukocyte Antigen (HLA) is known to be associated with RA in most ethnic groups. Some HLA-DR alleles are reported to be associated with RA susceptibility. A conserved amino acid sequence at position 70-74 (QKRAA, RRRRAA, or QRRAA) in HLA-DR $\beta$  chain is shared between the RA-associated HLA-DR alleles; this was designated as shared epitope (SE). A gene dosage effect was noted in the associations of SE alleles with susceptibility to RA in that homozygosity for SE alleles does confer higher disease risk and severity than heterozygosity for these alleles. HLA association study based on the amino acid residue revealed that three amino acid positions, 11, 71, and 74 in HLA-DR $\beta$  chain explained the susceptibility for RA. Extra-articular manifestations of RA include pericarditis, pleuritis, Felty's syndrome, vasculitis involving various organs, interstitial lung disease (ILD), and airway disease. Several studies have reported the association of extra-articular manifestations of RA with SE and DR4. ILD is frequently associated with RA and ILD in RA is one of the extra-articular manifestations with dismal prognosis. DR2 is associated with ILD in Japanese RA population. Significant associations of *HLA-DRB1\*08:02* with bucillamine-induced proteinuria and *HLA-A\*31:01* with methotrexate-induced interstitial lung disease were reported. These observations imply that HLA plays a substantial role in drug-induced hypersensitivity reactions. The molecular mechanisms underlying drug hypersensitivity associated with certain HLA alleles remain unclear.

### S9-6

#### Systems genetics for common diseases in post-GWAS era

Itsuro Inoue

National Institute of Genetics

Conflict of interest: None

With the advent of genome-wide association studies (GWASs), a large number of SNPs associated with human complex diseases and phenotypes have been reported. Most of the identified SNPs are located on intron or intergenic regions rather than coding regions, implying that the

SNPs are associated with the disease risk through the regulation of expression levels of nearby genes. Although recent studies from ENCODE project demonstrated that a large proportion of the SNPs identified by GWASs were located on open chromatin regions or DNase I hypersensitive sites (DHSs), regulatory mechanisms underlying these genotype-phenotype relationships remain to be elucidated. Here, we demonstrate our recent observation on the regulatory mechanism of a SNP on chromosome 9p21 that was associated with the risk of endometriosis by using functional genomics approaches. We first performed a target re-sequencing of 9p21 region for 48 Japanese individuals and constructed a linkage disequilibrium (LD) map. Combined with DNase-seq data in endometrial carcinoma cell lines, we identified three candidate SNPs that were in high LD with the GWAS hit and located on DHSs. Since these candidate SNPs were distant from 9p21 genes, we hypothesized that these SNP were on regulatory elements with enhancer activities through long-range chromatin interactions. Therefore, we performed chromatin conformation capture analysis and we observed that one of the candidate SNPs showed chromatin interaction with the promoter region of *ANRIL* in an allele specific manner. We found that the SNP disrupted a DNA binding motif of a transcription factor involved in Wnt signaling pathway. Finally, we demonstrated that the SNP was a *cis*-acting expression quantitative trait nucleotide of *ANRIL* by using allele specific expression analysis of normal endometrial tissues and endometrial carcinoma cell lines. These results may elucidate the regulatory mechanism underlying 9p21 endometriosis risk locus.

### S10-1

#### Current status and future prospects of vascularity assessment by ultrasound in rheumatoid arthritis

Shin-ya Kawashiri<sup>1,2</sup>, Atsushi Kawakami<sup>2</sup>, Kiyoshi Aoyagi<sup>1</sup>

<sup>1</sup>Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, <sup>2</sup>Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences

Conflict of interest: None

US can detect synovial hypertrophy and bone erosion by GS as well as abnormal vascularity by PD in synovial tissues of RA patients. The abnormal vascularity shows the activity of rheumatoid synovial inflammation. The great advantage of US is to be able to evaluate the vascularity of synovial tissues by non-invasive procedure. We and other investigators showed a PD positive synovitis is important for early diagnosis of RA and the prediction of progression to RA in UA patients. Furthermore, US synovitis score including vascularity may be useful for therapeutic monitoring because it can evaluate objectively the synovial disease activity. We have started the multi-center prospective cohort study of US in RA patients treated with biologic and targeted synthetic DMARDs in Kyushu area from June 2013. Therapeutic responsiveness and the differences between drugs will be analyzed. The presence of "subclinical synovitis" has been revealed by US. We previously reported the PD positive synovitis still remains in the substantial population of RA patients in clinical remission. Some previous reports showed the residual PD positive synovitis is independent predictor of structural progression and relapse. Meta-analyses of these studies revealed the associations of PD positive synovitis and risk of relapse and structural progression. The presence of PD positive synovitis before discontinuation of biologic DMARDs is a risk of relapse in RA patients during biologic-free remission. However, a part of patients without the PD positive synovitis have experienced relapses. Disappearance of PD signals may be necessary but not sufficient to sustain biologic-free remission. We will introduce new imaging techniques toward vascular assessment as future prospects. The first is a SMI (TOSHIBA), which can evaluate a fine blood flow of lower flow rate with high sensitivity. The second is an ICG-enhanced FOI (Xiralite), which can detect active synovitis with high sensitivity and in a short time.

### S10-2

#### Bone erosion: Present status and future outlook

Hideharu Sugimoto

Department of Radiology, Jichi Medical University School of Medicine

Conflict of interest: None



Articular bone erosion represents localized bone loss, initially involving cortical bone of bare area, which is natural barrier between the extra-skeletal tissue and the intertrabecular spaces of the bone marrow cavity. Although articular bone erosions were initially described more than 100 years ago, it is still a key element in the diagnosis and monitoring of RA. According to the ACR/EULAR 2010 classification criteria, a patient can be classified with RA in two ways. First, RA is diagnosed based on duration of symptom, physical examination, and laboratory findings without referring imaging findings. Radiographic evidence of bony erosion was intentionally omitted from the classification criteria to enable inclusion of early disease preventing circulatory logic. Second, a patient can be classified as RA when typical erosion is present in imaging such as plain radiograph. The EULAR task force has arrived at a cut-off for erosive disease of no fewer than three erosive joints to define RA. While erosion was one of the seven items of the 1987 ACR criteria, patients with typical erosion can be classified as having RA without fulfilling other criteria in the 2010 classification criteria. Although plain radiography is an inexpensive and commonly available technique of assessing bony erosions, it is the least sensitive modality for detecting them. Thus, a patient with inflammatory polyarthritis who has evidence of no erosion on plain radiographs may have erosions that can be identified by more sensitive techniques. Computed tomography (CT) is more sensitive than radiography and can be used to validate MRI erosion and can be considered as a standard of reference for detection of bone erosions in RA. Several emerging techniques are used to detect erosion; tomosynthesis, high-resolution peripheral CT, and X-ray phase imaging system. Of these techniques, tomosynthesis has been clinically used and demonstrated superiority over conventional radiography for the depiction of erosion.

### **S10-3**

#### **Diagnostic imaging for the patients with cervical instability secondary to rheumatoid arthritis**

Yoshihisa Sugimoto<sup>1</sup>, Keiichiro Nishida<sup>2</sup>, Masahiro Horita<sup>1</sup>, Kenzo Hashizume<sup>1</sup>, Masato Tanaka<sup>1</sup>, Toshifumi Ozaki<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Science of Functional Recovery and Reconstruction, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, <sup>2</sup>Department of Human Morphology, Science of Functional Recovery and Reconstruction, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

Conflict of interest: None

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disorder that can compromise the cervical spine in up to 40% of the cases. The purpose of treatment for RA patients is clinical remission or low disease activity, no radiographic progression, and normal function. We expect Non-biologic DMARDs and/or biologic DMARDs to prevent the progression of cervical instabilities. We performed a retrospective review about RA patients who had been treated in our hospital. This study focused on current status of diagnostic imaging such as radiographs, MRIs and enhance CTs. One hundred two patients with RA were reviewed. The mean disease duration was 20 years, the mean follow-up period was 34 months. The patients were divided into four groups by radiographic evaluation at the baseline of the study. Group A had no pre-existing cervical spine lesions, group B had AAS, group C had mild VS, and group D had severe VS. Group A to D consisted of 39, 20, 30, and 13 patients respectively. Radiographic progression was noted none in group A, 2 patients (10%) in group B, 6 (20%) in group C, and 3 (23%) in group D. We performed cervical fusion for 46 patients with RA for the past 10 years. There were 43 women and 3 men. Average follow-up periods were 2.5 years. Average duration of disease was 25 years (range 6 to 55 years). Three of 46 patients (7%) underwent surgery within 10 years after the onset. Enhance CTs and MR angiographies were useful for screening for abnormality of vertebral artery. Twelve patients (26%) had vertebral artery stenosis. In the MRI study, 17 patients (30%) showed fluid which was located around the dens. Number of surgeries has decreased by 75% for the past 10 years.

### **S10-4**

#### **Musculoskeletal ultrasound in the EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis**

Kei Ikeda

Department of Allergy and Clinical Immunology, Chiba University Hospital, Chiba, Japan

Conflict of interest: None

In 2013, EULAR published the EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis (Colebatch et al. *Ann Rheum Dis* 2013;72:804). The EULAR taskforce comprised of 19 experts from 13 countries first identified key clinically relevant questions, performed systematic literature review (SLR), made recommendations based on the SLR, and determined the strength/level of evidence of each recommendation, following appropriate process for developing guidelines. Out of the 10 recommendation items, 9 are related to musculoskeletal ultrasound, reflecting the wide use of this imaging modality in current daily practice. The recommendations show that ultrasound detects synovitis and bone damage more accurately than do clinical examination and plain radiograph, respectively (recommendation 3, 4). Given these superiorities, the recommendations indicate the use of ultrasound in the diagnosis (recommendation 1, 2), the prediction of joint damage progression (recommendation 5), the prediction of treatment response (recommendation 6), monitoring disease activity (recommendation 7) and joint damage (recommendation 8), and determining remission (recommendation 10) in the management of RA. However, the recommendations only provide concepts because the SLR results did not give consensus about the exact methods using ultrasound to improve the outcomes of RA management. Therefore, the taskforce identified future research agenda primarily to provide such standardized methods. In this presentation, the ultrasound part of the EULAR recommendations will be overviewed and issues which are not argued in the recommendations will also be discussed.

### **S10-5**

#### **EULAR recommendations for the use of MR imaging of the joints in the clinical management of rheumatoid arthritis**

Tamotsu Kamishima

Faculty of Health Science, Hokkaido University

Conflict of interest: None

Below is the simplified list of EULAR recommendations for the use of MR imaging of the joints in the clinical management of rheumatoid arthritis 1 When there is diagnostic doubt 2 To predict the progression to clinical RA from undifferentiated inflammatory arthritis 3 Detection of joint inflammation 4 If conventional radiographs do not show damage and may be used to detect damage at an earlier time point (especially in early RA) 5 MRI bone oedema and Joint inflammation (synovitis) for the prediction of further joint damage 6 To predict response to treatment 7 Monitoring disease activity 8 To monitor disease progression 9 Monitoring of the cervical spine 10 To detect inflammation that predicts subsequent joint damage, even when clinical remission is present These recommendations as well as the research agenda will be discussed in the symposium.

### **S10-6**

#### **The challenge of JCR-JCR ultrasound intermediate course-agenda for the future**

Shigeru Ohno

Yokohama City University Medical Center, Center for Rheumatic Diseases

Conflict of interest: None

The role of musculoskeletal ultrasound (MSUS) in the management of rheumatic diseases has been established based on numerous reports in the literature. On the other hand, there are still some obstacles to integrate MSUS into standard rheumatology practice. One of the reasons is the lack of opportunity of training. Training of MSUS can be achieved indi-

vidually from an expert, but training and education through ultrasound training courses is one of the most efficient and reasonable way. JCR has been offering fundamental MSUS courses for a couple of years, and since 2013, intermediate MSUS course has also been offered for JCR members. JCR MSUS courses is conducted in accordance to the EULAR recommendations for the content and conduct of EULAR Musculoskeletal Ultrasound Courses. The trainers of JCR MSUS courses have experience of MSUS examination under education at leading European centers and/or have the certification of trainers given at the EULAR train the trainer course. JCR MSUS courses offers an opportunity to learn MSUS techniques equivalent to EULAR courses. The role of MSUS must be different between clinical trials and daily clinical practice. In addition to the importance of MSUS in the serial evaluation of disease activity in limited patients participating in clinical trials, it is also, and probably more important to perform MSUS as part of an overall clinical evaluation in a rheumatology office that would include a history and physical examination (i.e., point of care MSUS). The establishment of the best practice of MSUS in routine clinical practice should result in the improvement of prognosis of all of the patients with rheumatic diseases.

### S11-1

#### Citrullinated antigen-specific T and B cells in RA

Vivianne Malmström

Karolinska Institutet, Stockholm, Sweden

Conflict of interest: Yes

Ever since the discovery 30 years ago of the genetic association of rheumatoid arthritis (RA) to a certain set of HLA-DR alleles and the demonstration of an abundant expression of such HLA class II molecules in the rheumatic joint, CD4<sup>+</sup> T cells represent a classical effector cell in RA. Still, the specificity of the T cells have remained only partly understood. The more recent recognition of antibody responses to the post-translational modification citrulline in the context of RA has allowed a renaissance in the studies of autoreactive lymphocytes. We have focused on autoantibody-positive and HLA-DR shared epitope allele positive RA patients to study the autoimmune components of the B and T cell repertoires. We study several citrullinated candidate autoantigens in parallel. Autoreactive B cells were found to be relatively abundant in the rheumatic joint. Autoreactive IgG have been expressed from synovial fluid, both from memory B cells and plasma cells, and the memory compartment held more autoreactive B cells than the plasma cells although the affinity of the plasma cell-derived antibodies exceeded that of the memory cell derived IgG. These recombinant monoclonal antibodies are currently being used for mechanisms of action studies. Autoreactive T cells were only found at very low frequencies, and by use of HLA-DR tetramers we can directly *ex vivo* enumerate and phenotype these cells. Surprisingly, we find very little evidence of autoreactive Th17 T cells, while Th1 cells are readily detectable. RA patients generally have a flora of autoreactive B and T cells with different fine specificities making it challenging to get a complete overview of the autoimmune repertoire. Future studies aiming at visualizing autoreactive T cells in newly diagnosed RA, or at risk individuals, will be important before antigen-specific tolerance protocols can be developed.

### S11-2

#### Dendritic cell targeting for citrullinated antigen-specific therapy in early and pre-rheumatoid arthritis

Ranjeny Thomas

University of Queensland, Brisbane, Australia

Conflict of interest: Yes

Disease modifying strategies are available for treatment of rheumatoid arthritis (RA), and good response rates are achieved. However, limitations include toxicity, a response rate ceiling, cost and rationing of biologic therapies, inability to cure or permanently reverse RA pathology, and inability to prevent disease. Recent evidence suggests that treatment of very early RA with immunomodulatory drugs can delay or attenuate disease onset. RA is strongly associated with the *HLA-DRB1* locus that possesses the "shared susceptibility epitope (SE)", and the citrullination of self-antigens. Approximately 80% of RA patients develop autoantibod-

ies targeted against citrullinated self peptides. These patients are more likely to have RA-associated HLA-DR risk alleles and to smoke. Using HLA-II tetramers, we demonstrated citrullinated vimentin and aggrecan-specific CD4<sup>+</sup> T cells in the peripheral blood of *HLA-DRB1\*04:01*<sup>+</sup> RA patients and healthy individuals, and cytokine responses *ex vivo*. In RA patients, the number of autoreactive cells correlated with disease activity, and the proportion of antigen-specific regulatory T cells was significantly lower than in healthy controls. We are developing antigen-specific immunotherapy to target dendritic cells (DC) *in situ* with liposomes encapsulating citrullinated peptide and NF- $\kappa$ B inhibitor. In a proof-of-concept trial, delivery of citrullinated peptide and tolerogenic DC was safe and had systemic immune effects. DC represent an important target for citrullinated peptide-specific immunotherapy in RA. HLA-II tetramer biomarkers will be essential to monitor such trials. Antigen-specific therapy has potential for prevention of RA in at-risk individuals with susceptibility genotypes and other risk factors and biomarkers predictive of disease.

### S11-3

#### Clinical aspects of citrullination in RA

Koichiro Ohmura

Kyoto University Graduate School of Medicine, Kyoto, Japan

Conflict of interest: None

Anti-CCP antibody (CCP Ab) is now an important biomarker for diagnosing RA. It is specific to RA and only 1.5 % of healthy subjects and ~5% of other collagen vascular/rheumatic disease patients are positive for CCP Ab, whereas ~80% of established RA is CCP Ab positive. In contrast, it has been reported that only ~60% of early RA patients are CCP Ab positive. Also CCP Ab is recognized years before the onset of RA. From these observations, it may be conceived that CCP Ab-negative RA develops into CCP Ab-positive RA. However, previous reports showed that only a part of CCP Ab-negative RA seroconvert to CCP Ab-positive. Our retrospective observations revealed that 5.4% of CCP Ab-negative RA seroconverts to CCP Ab-positive and all of them were RF-positive. Therefore, CCP Ab-negative RA consists of two distinct subsets. Next, we focus on the CCP Ab-positive non-RA collagen vascular diseases. We investigated whether CCP Ab-positive non-RA collagen vascular diseases developed erosive joint diseases retrospectively. Although there are some limitations, we found CCP Ab-positive non-RA patients do not develop erosive arthritis. Since there are reports that such CCP Ab-positive sera react to non-citrullinated flaggrin (anti-cyclic arginine peptide Ab: anti-CAP Ab), those patients may not react specific to citrullinated proteins. Thus, citrullinated proteins may be considered as very specific antigens to RA. We further investigated the CCP Ab-positive collagen vascular disease patients who fulfilled the 1987 ACR revised classification criteria for RA. We found many of them showed erosive arthritis, which indicates these patients have overlapped disease. Therefore, when the CCP Ab-positive non-RA collagen vascular disease patients fulfilled the 1987 ACR revised criteria, it is better to consider them as having RA and treat them as RA-other collagen vascular disease overlapped patients. In this symposium, the usefulness and the pitfalls of CCP Ab will be discussed.

### S11-4

#### The role of PADI4 in rheumatoid arthritis

Hirofumi Shoda<sup>1</sup>, Yu Seri<sup>1</sup>, Akari Suzuki<sup>2</sup>, Isao Matsumoto<sup>3</sup>, Takayuki Sumida<sup>3</sup>, Keishi Fujio<sup>1</sup>, Kazuhiko Yamamoto<sup>1</sup>

<sup>1</sup>Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, <sup>2</sup>Laboratory for Rheumatic Diseases, SNP Research Center, The Institute of Physical and Chemical Research (RIKEN), Yokohama, Japan, <sup>3</sup>Division of Clinical Immunology, Major of Advanced Biomedical Applications, Graduate School of Comprehensive Human Sciences, Tsukuba University, Tsukuba, Japan

Conflict of interest: None

Peptidylarginine deiminase type 4 (PADI4) polymorphism is a genetic risk of rheumatoid arthritis (RA). Its importance in anti-citrullinated peptide antibody (ACPA)-positive RA is investigated in view of antigen citrullination, whereas there were some reports describing the association between PADI4 and ACPA-negative RA. PADI4 can modify the nuclear

proteins and regulate gene expression and cell proliferation. Of note, PADI4 plays a pivotal role in the formation of neutrophil extracellular traps (NETs). NETs not only contain citrullinated histone, which is one of the ACPA targets, but also have a potential of helper T cell differentiation. In this way, we can hypothesize several pathways of PADI4 contributions to RA pathogenesis. Here, PADI4 knockout (KO) mice in DBA/1J background were generated, and tested in collagen-induced arthritis (CIA) and glucose-6-phosphate isomerase (GPI)-induced arthritis model. In each model, arthritis scores, histological scores, and serum antibodies were significantly decreased in PADI4 KO mice. In the joints of PADI4 KO CIA mice, the citrullination was not detected. In addition, serum IL-6 concentrations and Th17 cell differentiation were reduced after GPI-immunization in PADI4 KO mice. Importantly, after GPI immunization, the numbers of CD11b+ myeloid cells were significantly less increased in the spleens of PADI4 KO mice. We speculate that PADI4 could have an association with the survival of myeloid cells, which contributed to the reduction of arthritis severity. In conclusion, we newly demonstrated that PADI4 has multi-effects on immune systems besides antigen citrullination, and plays important roles in the acquired immunity and arthritis.

### S11-5

#### Citrullination of chemokines in the pathogenesis of rheumatoid arthritis

Ken Yoshida

Division of Rheumatology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan

Conflict of interest: None

Citrullination, catalysed by peptidylarginine deiminase (PAD), is a post-translational modification of arginine to citrulline, which contributes to the pathogenesis of rheumatoid arthritis (RA). Chemokines are highly expressed in RA joints, and PAD 2 and PAD 4 are present in synovial tissue. These facts support the hypothesis that cit-chemokines may be present in RA joints. Using a newly developed ELISA system, we examined whether ENA-78/CXCL5, MIP-1 $\alpha$ /CCL3, and MCP-1/CCL2, which are representative chemokines in RA, are citrullinated in RA biological fluids, and if so, what their biological activities are. In our study, the ELISA showed that citENA-78/CXCL5, citMIP-1 $\alpha$ /CCL3, and citMCP-1/CCL2 were all significantly higher in RA sera than in normal control sera. Furthermore, citENA-78/CXCL5 and citMIP-1 $\alpha$ /CCL3 were significantly higher in RA SF than in either osteoarthritis (OA) SF or other rheumatic diseases (OD) SF. We also found significant positive correlations between citENA-78/CXCL5 and CRP as well as between citENA-78 and ESR, whereas ENA-78/CXCL5 did not correlate with any clinical parameters examined. Normally, ENA-78/CXCL5 is a neutrophil chemotactic factor. However, the *in vitro* chemotaxis assays showed that citENA-78/CXCL5 acquired a monocyte recruiting function that non-citENA-78/CXCL5 did not. In addition, the chemotaxis assays demonstrated that citENA-78/CXCL5 recruits monocytes via both CXCR2, which is the primary ENA-78/CXCL5 receptor, and CXCR1, which has 78% homology at the amino acid level with CXCR2. These results suggest that citrullination of ENA-78/CXCL5 can alter its receptor affinity and cellular recruitment properties. The *in vivo* experiment showed that citENA-78/CXCL5 results in increased inflammation and monocyte migration in mouse knee joints compared to non-citENA-78/CXCL5. Our data suggest that citrullination enhances the proinflammatory activity of ENA-78/CXCL5 and accelerates disease progression in inflammatory arthritis.

### S12-1

#### The indication and surgical results of shoulder arthroplasty comparing between three techniques; hemiarthroplasty, total shoulder arthroplasty and reverse shoulder arthroplasty

Takuji Iwamoto<sup>1</sup>, Noboru Matsumura<sup>1</sup>, Takeshi Mochizuki<sup>3</sup>, Kensuke Ochi<sup>1</sup>, Kazuki Sato<sup>1</sup>, Hiroyasu Ikegami<sup>2</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Keio University School of Medicine, <sup>2</sup>Department of Orthopaedic Surgery, Toho University Ohashi Medical Center, <sup>3</sup>Department of Orthopaedic Surgery, Kamagaya General Hospital

Conflict of interest: None

Implant arthroplasty is indicated for the treatment of shoulder joint disorder, including severe pain and restriction of range of motion, in patients with rheumatoid arthritis (RA). There are two types of arthroplasty, one is total shoulder arthroplasty (TSA), which involves the replacement of both the humeral head and the glenoid and the other is hemiarthroplasty (HA), which is the replacement of humeral head. Compromised bone and soft tissue due to the severity of RA make the decision between TSA and HA a controversial choice. It is important to know the characteristics of TSA and HA, since each procedure has the advantages and disadvantages. The problem of TSA is the difficulty of the replacement of glenoid and loosening of the glenoid component according to the upper migration of the humeral head in the long term. The problem of HA is the risk for revision by painful glenoid erosion. It is generally accepted that condition of the rotator cuff is important to making a decision. Sperling JW et al reported the long term results comparing TSA and HA of 303 shoulders in 247 RA patients. Although there was significant long term pain relief and improvement of range of motion both TSA and HA, TSA was superior for pain relief, improvement in abduction, and lower risk of revision surgery among patients with an intact rotator cuff. In addition, the new concept of reverse shoulder arthroplasty (RSA) has become a well established procedure for the treatment of glenohumeral osteoarthritis with massive rotator cuff deficiency. Although the indications for RSA in RA patients have not been well defined, RSA has the potential to improve the postoperative shoulder elevation even in patients with severe arthritis by the function of deltoid muscle. The purpose of this presentation is to review our experience with TSA and HA in RA patients, and to discuss the current indication including RSA with literature-based review.

### S12-2

#### Surgical efficacy and complications of reconstructive surgeries for the treatment of RA wrists

Norimasa Iwasaki<sup>1</sup>, Makoto Motomiya<sup>2</sup>, Tatsuya Masuko<sup>3</sup>, Jyunichi Ishikawa<sup>4</sup>, Yuichiro Matsui<sup>1</sup>, Tadanao Funakoshi<sup>1</sup>, Akio Minami<sup>5</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Kushiro Rosai Hospital, Kushiro, Japan, <sup>3</sup>Department of Orthopaedic Surgery, Steel Memorial Muroran Hospital, Muroran, Japan, <sup>4</sup>Teine Seikeigeka Rehabilitation Clinic, Sapporo, Japan, <sup>5</sup>Hokkaido Chuo Rosai Hospital Sekison Center, Bibai, Japan

Conflict of interest: None

The main purpose of reconstructive operations for RA wrists is to achieve painless and stabilized wrist joints. Currently, limited wrist fusions are widely accepted as an effective reconstructive procedure. The authors have performed radiolunate fusion for the Larsen grade II to IV cases with ulnar shift of carpal bones, preservation of midcarpal joint, and relatively young age. Our previous study demonstrated that this procedure provided acceptable clinical and radiographic outcomes against such RA wrist joints. However, the authors found a significant decrease in wrist motion postoperatively. To overcome this limitation, we have developed a novel total wrist replacement implant. Although several total wrist replacement implants have been developed for RA wrists, no acceptable outcomes have been achieved due to early loosening or implant failure after operation. The basic concept for developing the novel implant is to simulate the dart throwers motion in living wrist joints after performing total wrist arthroplasty. To achieve this motion, we designed a semiconstrained type implant, which reconstruct the joint line at the level of midcarpal joint. The authors have already collected the basic and clinical data for clinical approval of the developed implant. The author will present the previous data focusing on the topics described above.

### S12-3

#### Metacarpophalangeal Joints arthroplasty in Rheumatoid Arthritis

Shosuke Akita, Hideki Tsuboi, Shigeyoshi Tsuji, Jun Hashimoto, Masanobu Saito

Department of Orthopedic Surgery, Osaka Minami Medical Center

Conflict of interest: None

**[Objective]** We perform reconstruction of the soft tissue alone in rheumatoid arthritis patients with mild ulnar drift, who maintain articular cartilage on imaging examinations. We perform arthroplasty with a silicone implant in patients who show narrowing of the joint space or palmar subluxation of the proximal phalanx on imaging examinations. We herein present the outcomes of these procedures. **[Subjects and Surgical Procedures]** Reconstruction of soft tissue alone was performed in 30 fingers of 9 hands in 7 patients (soft tissue reconstruction group). For the surgical technique, lateral band release was first performed on the ulnar side, followed by drilling in the proximal phalanx, and the dislocated extensor tendon was reduced to the original position. Subsequently, the tenodesis to the proximal phalanx was performed without performing tenotomy. In addition, a silicone implant arthroplasty (Avanta PreFlex) was performed in 90 fingers of 25 hands in 19 patients (mean age at the time of surgery: 67 years old) (silicone group). **[Outcome]** The mean postoperative follow-up period was 30 months (range: 12-51 months) in the soft tissue reconstruction group. The mean MCP flexion/extension angles were 85°/39° preoperatively and 80°/23° at the time of postoperative examination, showing that flexion of the MCP joint was maintained. In addition, the ulnar deviation angles at preoperative/postoperative time points were 22°/10°, indicating an improvement. The mean postoperative follow-up period was 21 months in the silicone group. In this group, the mean MCP flexion/extension angles were 77°/44° preoperatively and 66°/13° at the time of postoperative examination, demonstrating that many patients had achieved MCP flexion  $\geq 60^\circ$ . In addition, the mean ulnar deviation angles at preoperative/postoperative examinations were 33°/6°, indicating an improvement. **[Conclusion]** Our procedures for ulnar drift are useful methods in rheumatoid arthritis patients.

#### **S12-4**

##### **Update in joint-preserving surgery for rheumatoid forefoot deformity**

Koichiro Yano, Katsunori Ikari, Shigeki Momohara  
Department of Orthopedic, Institute of Rheumatology, Tokyo Womens Medical University, Tokyo, Japan

Conflict of interest: None

Although the introduction of powerful anti-rheumatic drugs has dramatically improved the treatment of rheumatoid arthritis (RA), many patients still experience progressive joint destruction. Painful forefoot deformities are prevalent in 80-90% of patients with RA, many of whom undergo surgery to treat them. A variety of surgical procedures have been performed for forefoot deformities in patients with RA. Some of these procedures, such as arthrodesis or resection arthroplasty, require that the function of the MTP joint be sacrificed. Recently, the paradigm shift of RA treatment led us to reconsider the benefits of joint preservation. In 2010, we developed rotational closing-wedge osteotomy of the first metatarsal, which corrects varus and rotational deformities of the first metatarsal. We previously reported the positive results of this procedure in 2013. We have been performed a modified oblique shortening osteotomy for lesser toe deformities. The amount of shortening of the lesser metatarsals is selected by considering the degree of the dislocations and contractures of the metatarsophalangeal joints. The modified oblique shortening osteotomy procedure for lesser toe deformities often causes non-unions at the sites of osteotomy, but we have successfully reduced the rates of the non-union significantly through several efforts during surgery. The first aim of this presentation is to describe the surgical procedure in detail and to assess the short-term subjective, functional, and radiographic results of this joint-preserving procedure for patients with RA. The second aim is to consider the cause of and preventative methods for the unique complications of forefoot surgery in RA patients. The third aim is to present the latest findings and problems of joint-preserving surgery for rheumatoid forefoot deformities by summarizing previous reports.

#### **S12-5**

##### **Total ankle arthroplasty -Intermediate and long term clinical results, complications and revision surgery -**

Ryota Hara<sup>1,2</sup>, Yasuhito Tanaka<sup>1,2</sup>, Akira Taniguchi<sup>2</sup>, Yasunori Kobata<sup>1,2</sup>  
<sup>1</sup>The Center for Rheumatic Diseases, Nara Medical University, Nara, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Nara Medical University, Nara, Japan

Conflict of interest: None

As the paradigm shift occurred in pharmacotherapy for rheumatoid arthritis (RA) in the last decade, surgical treatment must be aimed better quality of life, especially for long-term affected patients. Since weight-bearing joints, such as the hips, knees, ankles and subtalar joints are strongly associated with walking ability. If reconstructive surgery was made, excellent long term results and remarkable improvement of the function are necessary. Although total hip and knee arthroplasties have good long term survival rate and function, results of total ankle arthroplasty were not well satisfied and arthrodesis of ankle and/or subtalar joint are often indicated. Because bony ankylosis is frequently observed in the RA tarsal joints, arthrodesis may lead to pantalar fusion, which caused remarkable limitations of activity of daily living. We preferred total ankle arthroplasties (TAA) for end-stage ankle arthritis. We have used two-component alumina prosthesis (TNK ankle) since 1991. The tibial prosthesis coated with calcium phosphate paste and bone marrow obtained by puncture of the iliac bone was fixed to the posterior cortex of the tibia using a small screw, and the talar prosthesis was fixed with cement in recent years. Because the major cause of the revision surgery after TAA was severe subsidence of the talar prosthesis, our first choice of salvage surgery after TAA is revision TAA using the third generation whole body prosthesis of the talus. We can expand the indication of TAA for the case with collapse of the talus by using total talar prosthesis, however, for the patients with malalignment or young patients, arthrodesis of ankle and/or subtalar joint could be better. In this symposium, we would like to report clinical results of TAA in our medical school.

#### **S13-1**

##### **Toward Next Generation Rheumatology: pathogenesis of RA and its subsets**

Lars Klareskog  
Rheumatology Unit, Department of Medicine, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

Conflict of interest: None

Rheumatoid arthritis (RA) is one of several inflammatory rheumatic diseases, which are defined by clinical criteria, and where studies on etiology and pathogenesis have demonstrated that several different molecular pathways are involved, and where different variants of the disease can be initiated by different combinations of genetic and environmental factors. The development of new approaches to prevention and treatment of RA and other rheumatic diseases will be highly dependent on our abilities to identify the different variants of RA. Better knowledge of triggering factors will allow better prevention. Better knowledge about molecular pathways that drive different subsets of disease will allow us to identify which pathways are used in different individuals and help to develop and test new approaches to specifically interfere with these disease-inducing pathways, which may differ profoundly between patients/individuals. Examples of how to approach these challenges will be provided from studies of RA, using a combination of epidemiology, genetics and molecular immunology, and with the view that RA represents a spectrum of conditions where pathology develops gradually, and where understanding of this gradual development provides many new options for prevention as well as potentially curative therapies.

#### **S13-2**

##### **Asia-Pacific League of Associations for Rheumatology (APLAR) and the Next Generation of Rheumatologists and Rheumatology**

Kevin D Pile  
APLAR President, Department of Medicine, University of Western Sydney, Sydney, Australia

Conflict of interest: None

Over the last 50 years, APLAR has grown to represent over 30 countries which encompass over half of the world's population. APLAR represents a small fraction of the world's rheumatologists who provide rheumatic and musculoskeletal disorder care to this immense group. Member countries cover the spectrum of World Bank income bands, with varying ratios of rheumatologists: patients and quite marked variation in training

and research opportunities, and treatment resources. Non-communicable diseases are coming to the forefront of health planning as the Global Burden of Diseases places Musculoskeletal Disorders as a major cause of Years lived with Disability with its impact on reduced contribution to the nations GDP and drain on health care and social support. APLAR has thrived during several generational changes and I am optimistic that the next generation of rheumatologists from all of its members countries will simultaneously contribute and derive benefit from their association with APLAR. Conversion of my optimism to actuality will occur by: 1. Sharing of research and clinical challenges 2. Provision of research and clinical fellowships/scholarships 3. Mentoring and partnership of rheumatology and musculoskeletal medicine training for rheumatologists, primary care physicians, and health workers 4. Strategic planning, listening and involvement of the next generation 5. Alignment with regional leagues and national/international groups to create a globally unified strategy for mitigation of Rheumatic and Musculoskeletal Disorders (RMDs)

### S13-3

#### Toward Next Generation Rheumatology: can basic research deliver?

Iain McInnes

Institute of Infection, Immunity and Inflammation, University of Glasgow, Scotland, UK

Conflict of interest: Yes

In the last decade there has been unprecedented progress in understanding many inflammatory rheumatic diseases. Developments have been based on improved understanding of pathogenesis, novel targets emerging as a consequence and also of altered strategic approaches to the management of common rheumatic diseases captured in the 'treat to target' concept. Much unmet need remains – few rheumatic diseases can be cured, and for most patients remission is not often attained and even then must be maintained by long term drug therapeutics. How might the next decade be transformed? I shall use the common inflammatory arthropathies to define a variety of approaches that may alter the landscape of treatment of rheumatic diseases. I shall draw examples mainly from the basic to translational literature. Firstly with the advent of ever more sophisticated molecular and bioinformatics approaches to disease discovery we will elucidate novel pathways - a major challenge will be to define which offer real clinical utility. This effort will benefit from the development of better characterised cohorts of patients in whom deep phenotyping and polyomic medicine approaches will be better able to define disease prognosis, natural history and thus the core driving mechanistic pathways – in essence we will better use pathology resolution to determine the critical molecular targets that offer hierarchical benefit in terms of drug development and biomarker lead stratification. The biotechnical development area will also offer novel modalities of intervention e.g. peptides delivered orally or via sophisticated parenteral deliver modalities which will facilitate formal dose optimisation and adjustment. Cellular therapies may render immune tolerance achievable. Outcome measure will also change based on biomarker based approaches such that we can define a molecular taxonomy of disease and outcome. In turn these will move the management of chronic rheumatic diseases to a remission induction and maintenance models that can prevent damage and render long-term outcomes secure.

### S13-4

#### Toward Next Generation Rheumatology: from clinical research to understanding and back

Tom W Huizinga

Leiden University Medical Center, Leiden, The Netherlands

Conflict of interest: None

Rheumatoid Arthritis (RA) is a chronic inflammatory and destructive disease. The phases of its development are now well defined ranging from the mere presence of genetic risk factors to full-blown persistent RA. We expect that the management of RA will change by testing intervention strategies designed to prevent the development of persistent RA. The likelihood of an individual at risk in different pre-RA phases progressing to RA is currently being defined. The subjects at the highest risk of developing arthritis (i) suffered from joint pain prior to showing typi-

cal joint swelling; (ii) experienced sick leave rising sharply already 6 months before the diagnosis; (iii) displayed elevated levels of systemic markers of inflammation and autoantibodies; and (iv) showed anatomical changes detected by advanced in vivo imaging. The strategies to detect patients at risk have been developed. Interventional studies in undifferentiated arthritis and early RA patients aiming to reach clinical remission as defined by the absence of signs and symptoms, already showed that drug free remission can be achieved if patients are treated very early. The development of specific autoantibody profiles and the selection of B-cells specific for citrullinated antigens and subsequent specific mutations from germline sequences are now identified, opening the possibilities for more specific interventions in early disease. An ideal intervention would be one that prevents the expression of the clinical entity we recognise as full-blown RA. Such intervention will halt the disease process in individuals from the 'phases' from the *pre-clinical status* [an individual with genetic risk factors & environmental risk factors that develops systemic autoimmunity] through the *clinical phases* [an individual will develop symptoms e.g. joint pain and stiffness, then arthritis finally to a disease to classified as RA.

### S13-5

#### SLE: From Biology to Therapeutic Targets, A T-Cell Journey

Joseph Craft

Yale University, New Haven, CT, USA

Conflict of Interest: Yes

Pathogenic CD4<sup>+</sup> T helper (Th) cells are critical for disease promotion in systemic lupus erythematosus (SLE, lupus). These cells exert their effector function via autoreactive B cell help in secondary lymphoid organs or by infiltration of tissues, such as the kidney. In both cases, autoantibody production and Th-cell infiltration, activation of innate immune cells ensues, mediated by autoantibody-autoantigen complex engagement and by tissue delivery of contact-dependent and soluble factors. The consequent inflammation leads to organ dysfunction and, sometimes, its loss. Thus, dissecting signals that promote CD4<sup>+</sup> Th-cell differentiation and maintenance in lupus is critical for understanding pathways of disease initiation and progression, and for identification of new therapeutic targets, or confirmation of existing ones. The signals that promote development and maintenance of CD4<sup>+</sup> Th cells in conventional immune responses have been defined, with parallel dissection ongoing in SLE. These studies in normal and autoimmune individuals have identified several nodes by which T cells have been, or can be, successfully targeted therapeutically in disease, including signals needed for activation, differentiation, and effector function. Future studies will rely upon dissection of T cell activation and function, using computational analyses to identify genetic precipitants and their associated molecular pathways leading to variations in functional readouts and disease phenotype, combined with repurposing of, design of new, therapeutics to interrupt these pathways.

### S13-6

#### Novel therapies

Josef S. Smolen

Medical University of Vienna, Austria

The therapeutic success experienced by so many patients with rheumatoid arthritis (RA) today rests on five parallel advancements that occurred over the last 20 to 25 years: (i) the optimized use of methotrexate which continues to be the anchor drug in RA; (ii) the development of reliable outcome tools; (iii) the advent of therapies interfering with highly specific molecules involved in pathogenetic events; (iv) early diagnosis of RA; and (v) the institution of a treatment-to-target strategy. Nevertheless, a considerable proportion of patients still do not achieve the treatment target due to insufficient response or safety issues. Therefore, new therapies are needed. Several new therapies are currently in development. Among these are biological agents which target, for example, IL-6, granulocyte-monocyte stimulating factor or interferon alpha, as well as targeted synthetic disease modifying antirheumatic drugs, such as Janus kinase inhibitors and blockers of other signal transduction pathways. One of these agents, tofacitinib, is currently already approved and used in many countries. The promise that these agents may carry will be discussed in detail.

## S14-1

### Management of respiratory infections under biologics treatment

Hitoshi Tokuda<sup>1,2</sup>

<sup>1</sup>Japan Community Healthcare Organization Tokyo-Yamate Medical Center, Tokyo, Japan, <sup>2</sup>Institute of Rheumatology Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

The introduction and wide use of biologics has changed dramatically the clinical course and prognosis of rheumatoid arthritis (RA) patients. But, as adverse events, increased risk of serious infections, especially those occurring in respiratory organs, have emerged as the most important obstacles against the safe use of this exquisite therapy. To solve this problem, we must pay special notice to the underlying diseases seen frequently in RA patients, that is, airway diseases (AD) and interstitial lung diseases (ILD). AD, such as bronchiectasis or bronchiolitis, is reported to exist in frequency of 30 or 40% of RA patients, through studies using HRCT. ILD are also found in 20 or 30%. These lung underlying diseases are now regarded as one of the extra-articular manifestations of RA. Through the analysis of bacterial pneumonia in RA patients, AD or ILD has been found as one of the major risk factors. The same tendency is also observed in Pneumocystis pneumonia (PCP) or in Non-tuberculous mycobacteriosis (NTM). Under the biologics treatment these tendencies are accentuated more and more. Taking these into considerations, management of lung infections in RA patients, especially under biologics therapy, should be strategic. For example, causative agents of pneumonia in patients with bronchiectasis are known to be different from those in general population. *Pseudomonas* is a prevailing pathogen. Accordingly we must choose antibiotics which are potent against this bacterium. As for PCP, it has been well established that lung impairment are caused by severe inflammation, the result of intense immune response against this organism. With this knowledge in hands, we must utilize adjunctive corticosteroid as early as possible and in sufficient dose, in parallel with antibiotics. With these knowledge and strategies we can hope relatively good prognosis in these potentially lethal complications

## S14-2

### Management of skin infections under immunosuppression

Hideo Asada

Nara Medical University, Nara, Japan

Conflict of interest: None

Recently, various biologics for immune diseases such as collagen diseases and rheumatoid arthritis, have been developed one after another. These drugs exert surprising therapeutic effects, and have become a great help for the patients suffering from incurable diseases. On the other hand, these new drugs cause immunosuppression, resulting in increase of various infectious diseases. In dermatology field, cutaneous infection of various microorganisms causes various skin diseases, for example, fungal infections such as ringworm or candidiasis, bacterial infections such as furunculosis or cellulitis, and viral infections such as herpes zoster. In particular, under immunosuppression, many patients exhibiting severe skin conditions than usual, and clinical symptom often become worse rapidly. In recent years we tend to increasingly encounter severe skin infection, such as necrotizing fasciitis requiring urgent debridement and systemic management. Therefore, precise diagnosis of early stage is essential in the treatment of infectious diseases under immunosuppression. In order to not miss the signs of cutaneous infection, we need to know characteristics of principal infectious diseases of skin and to keep paying attention to changes in the skin of the patients on a regular basis. In this lecture, I present several typical cases of skin infection under immunosuppressive condition, and try to explain the points of diagnosis and treatment.

## S14-3

### Prevention of Surgical Site Infection in Joint Surgery

Kazuhiko Matsushita<sup>1</sup>, Satoshi Abe<sup>2</sup>, Tomoo Ishii<sup>3</sup>, Shiro Kajiyama<sup>4</sup>, Akihiro Kotani<sup>5</sup>, Masakatsu Saitoh<sup>6</sup>, Toshinori Masaoka<sup>7</sup>, Kouji Yamada<sup>8</sup>, Toru Suguro<sup>9</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Kawasaki Municipal Tama Hospital, Kawasaki, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Teikyo Uni-

versity School of Medicine, <sup>3</sup>Department of Orthopedic Surgery, Ibaraki Medical Center, Tokyo Medical University, <sup>4</sup>Department of Orthopaedic Surgery, Nagasaki University, <sup>5</sup>Department of Orthopaedic Surgery, Kyorin University School of Medicine, <sup>6</sup>Department of Orthopaedic Surgery, PL Hospital, <sup>7</sup>Department of Orthopedic Surgery, Tokyo Medical University, <sup>8</sup>Department of Orthopedic Surgery, Kanto Rosai Hospital, <sup>9</sup>Japan Research Institute of Artificial Joint

Conflict of interest: None

Patients with rheumatoid arthritis are considered immunocompromised hosts. Several papers suggest that rheumatoid arthritis was a risk factor for surgical site infection (SSI) after artificial joint replacement. Many papers suggest that the use of biological preparations will not cause severe SSI if a suitable waiting period is set. However, care should be taken as the use of biological preparations can pose a risk to artificial joint replacement. It was thought that exogenous bacteria such as airborne bacteria during surgery cause SSI. However, it has recently been reported that in 85.7% of patients who undergo orthopedic surgery and who develop deep SSI, *Staphylococcus aureus* in the nasal cavity and infection site had the same genotype, which suggests that endogenous bacteria carried by the actual patient can cause SSI. Recent reports indicate that preoperative sterilization of the nasal cavity and skin of the entire body reduces the incidence of SSI. However, no subjects or methods have been established to effectively screen for bacteria carried in the nasal cavity, such as *S. aureus* including MRSA. On the other hand, there are 2 contrasting opinions regarding preventive administration of anti-MRSA agents, some believe that it should be indicated for individuals carrying MRSA, whereas others believe that it should be administered to immunocompromised hosts irrespective of the bacteria carried. With the former, the issue remains as to how and where to check for the presence or absence of MRSA, while for the latter, there is insufficient evidence. In patients with rheumatoid arthritis, the carriage rate of *S. aureus* including MRSA in the nasal cavity, and how to screen for bacteria carried in the nasal cavity should be examined in future. Prevention methods of SSI in arthroplasty for rheumatic disease will be presented.

## S14-4

### Basic and clinical issues on vaccines in the prevention of infection

Minoru Satoh

Department of Clinical Nursing, University of Occupational and Environmental Health, Kitakyushu, Japan

Conflict of interest: None

Vaccines often contain adjuvants to enhance immune response to their microbial components. Adjuvants are known to show their effects via activation of toll-like receptors (TLR) and other innate immune pathways, however, detail mechanisms remain to be clarified. TLR and type I interferons (I-IFN) that are important in the vaccine adjuvant activity also play a key role in the pathogenesis of SLE and other autoimmune diseases. Thus, the same receptors and pathways are involved in vaccination and autoimmune diseases. Induction of TLR7- and I-IFN-dependent lupus-like autoimmune syndrome by adjuvant oils in mice and vaccination-induced systemic autoimmune disease in farmed salmon, have been reported. Concerns on possible induction of autoimmune diseases by vaccination have been raised for many years despite lack of clear evidence from most epidemiological studies. Recently, vaccination-related autoimmune diseases have been described as a part of ASIA (autoimmune syndrome induced by adjuvants), though the causal relationship and definition are not very clear. There are many issues to be considered in the vaccinations in systemic autoimmune diseases. For example, whether the efficacy of vaccination is comparable to healthy individual and when vaccination should be considered in patients under steroid, immunosuppressive therapy or biological. Also, whether the type and prevalence of adverse events of vaccination in patients with systemic autoimmune disease and whether the vaccination that can affect immune cells and cytokines can exacerbate the autoimmune diseases or affect efficacy of treatment. On the other hand, vaccination need to be considered for pneumococcus, influenza and herpes zoster among patients with systemic autoimmune diseases. Basics of vaccination and vaccine adjuvants and their interaction with immune abnormalities in systemic autoimmune diseases and current status of vaccination, issues to be considered and future

direction will be discussed.

## S15-1

### Genetic background of ANCA-associated vasculitis in the Japanese population

Naoyuki Tsuchiya<sup>1</sup>, Narumi Hasebe<sup>1</sup>, Misaki Hidaka<sup>1</sup>, Ken-ei Sada<sup>2</sup>, Shigeto Kobayashi<sup>3</sup>, Hidehiro Yamada<sup>4</sup>, Hiroshi Furukawa<sup>5</sup>, Kunihiro Yamagata<sup>6</sup>, Takayuki Sumida<sup>7</sup>, Nobuyuki Miyasaka<sup>8</sup>, Shigeto Tohma<sup>5</sup>, Shoichi Ozaki<sup>4</sup>, Seiichi Matsuo<sup>9</sup>, Hiroshi Hashimoto<sup>10</sup>, Hirofumi Makino<sup>11</sup>, Yoshihiro Arimura<sup>12</sup>, Masayoshi Harigai<sup>8,13</sup>, Aya Kawasaki<sup>1</sup>

<sup>1</sup>Molecular and Genetic Epidemiology, Faculty of Medicine, University of Tsukuba, <sup>2</sup>Department of Medicine and Clinical Science, Okayama University, <sup>3</sup>Department of Internal Medicine, Juntendo University Koshigaya Hospital, <sup>4</sup>Department of Internal Medicine, St Marianna University, <sup>5</sup>Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami National Hospital, Sagami, Japan, <sup>6</sup>Department of Internal Medicine (Nephrology), University of Tsukuba, <sup>7</sup>Department of Internal Medicine (Rheumatology), University of Tsukuba, <sup>8</sup>Department of Medicine and Rheumatology, Tokyo Medical and Dental University, <sup>9</sup>Department of Nephrology, Nagoya University, <sup>10</sup>Juntendo University School of Medicine, <sup>11</sup>Okayama University Hospital, <sup>12</sup>First Department of Internal Medicine, Kyorin University School of Medicine, <sup>13</sup>Department of Pharmacovigilance, Tokyo Medical and Dental University

Conflict of interest: None

Striking difference is observed in the incidence of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) subsets between European and Japanese populations. Granulomatosis with polyangiitis (GPA) and proteinase 3 (PR3)-ANCA positive AAV are prevalent in the European populations, while microscopic polyangiitis (MPA) and myeloperoxidase (MPO)-ANCA positive AAV are dominant in the Japanese. We have been conducting a multicenter collaboration study on the genetics of AAV in the Japanese. Thus far, we identified *HLA-DRB1\*09:01-DQB1\*03:03* as a risk haplotype for MPA and MPO-ANCA positive AAV. Of interest, this haplotype is common in the East Asian populations, but rare in the European populations. On the other hand, genome-wide and candidate gene studies in Europe and in north America reported association of *DPB1\*04:01* with GPA. The frequency of this allele is much higher in the European populations than in East Asians. In this talk, I will update the *HLA-DRB1* and *DPB1* allele typing data on 356 Japanese patients, the largest sample size so far in the Asian AAV. We confirmed association of *DRB1\*09:01* with MPA and MPO-ANCA positive AAV; in addition, we detected a protective effect of *DRB1\*13:02* against MPA and MPO-ANCA positive AAV. With respect to PR3-ANCA positive AAV, a trend toward increase was detected in *DPB1\*04:01*, as in the European populations; however, *DPB1\*04:01* was decreased in MPO-ANCA positive AAV, which was attributable to linkage disequilibrium with *DRB1\*13:02*. In the Japanese, about half of the patients with GPA were positive for MPO-ANCA. Interestingly, association with *DPB1\*04:01* and *DRB1\*09:01* was detected only in PR3-ANCA positive and MPO-ANCA positive AAV, respectively. These results supported the hypotheses that the population difference in HLA-class II allele frequencies may partly explain the population difference in the AAV subsets, and that HLA may be more strongly associated with ANCA specificity than with clinical classification.

## S15-2

### NETs-ANCA vicious cycle in MPO-ANCA-associated vasculitis

Akihiro Ishizu

Faculty of Health Sciences, Hokkaido University

Conflict of interest: None

**Objectives:** MPO-ANCA-associated vasculitis (MPO-AAV) is small vessel vasculitis with production of MPO-ANCA. A unique cell death of neutrophils, neutrophil extracellular traps (NETs), which is characterized by the release of chromatin fibers and intra-cytoplasmic proteins, including MPO, has recently been discovered. Although NET is an essential innate immune system, the disordered NETs could be related to autoimmune diseases. The aim of this study is to reveal the NET-related

production mechanism of MPO-ANCA and the pathogenesis of MPO-AAV. **Methods:** An anti-thyroid drug, propylthiouracil (PTU), is known as a risk to induce MPO-ANCA. We examined whether PTU would influence the NET formation induced by phorbol myristate acetate (PMA) and degradation of NETs by DNase I, which is an endogenous regulator of NETs. In addition, we examined whether the NETs generated by PMA with PTU would induce MPO-ANCA production and MPO-AAV development in vivo. Furthermore, the NET induction and NET degradation abilities of sera from patients with MPO-AAV were determined. **Results:** Abnormal formation and impaired degradation of NETs induced by PMA with PTU was involved in the pathogenesis of MPO-AAV. On the other hand, IgG eluted from MPO-AAV sera demonstrated high ability for NET induction. In addition, low ability of MPO-AAV serum for NET degradation was determined. Correspondingly, activity of DNase I was generally low in MPO-AAV. Furthermore, the presence of anti-NETs antibodies was demonstrated in some MPO-AAV sera. **Conclusions:** These findings suggested that NETs could be apt to remain in people with low DNase I activity in the serum. The persistent NETs could induce the production of MPO-ANCA, and MPO-ANCA could induce further NET formation through the direct action and indirect induction of the NET protective antibodies such as anti-NETs antibodies. Therefore, "NETs-ANCA vicious cycle" could be critically involved in the pathogenesis of MPO-AAV.

## S15-3

### Implication of sequential ANCA measurements in ANCA-associated vasculitides

Jan Willem Cohen Tervaert

Maastricht University, Maastricht, the Netherlands

Conflict of interest: None

ANCA titers [either directed to proteinase 3 (=PR3-ANCA) or to myeloperoxidase (=MPO-ANCA)] may predict disease activity suggesting a pathophysiological role for ANCA. The value of measuring ANCA during follow-up to predict a relapse is, however, controversial. Absolute titers correlate only weakly with disease severity, whereas we found that rising titers of ANCA occurring during clinical remission clearly predict relapses in patients with GPA and/or MPA. The close relation between ANCA and relapses, however, could not be confirmed in several other cohorts. On the basis of recently obtained pathophysiologic insights, we postulated that measuring ANCA is useful in patients with renal involvement but is less valuable in patients with nonrenal disease. One hundred sixty-six consecutive patients with ANCA-associated vasculitis, positive for either proteinase 3 (PR3)-ANCA or myeloperoxidase (MPO)-ANCA, were included in our study, followed at regular intervals, and tested for PR3-ANCA and MPO-ANCA. In this cohort, 104 patients had renal involvement (72 with PR3-ANCA, 32 with MPO-ANCA) and 62 patients had nonrenal disease (36 with PR3-ANCA, 26 with MPO-ANCA). During an average ( $\pm$ SD) follow-up of 49 $\pm$ 33 months and 18 $\pm$ 14 ANCA measurements, 89 ANCA rises and 74 relapses were recorded. ANCA rises correlated with relapses in patients who presented with renal involvement (hazard ratio [HR], 11.09; 95% confidence interval [95% CI], 5.01 to 24.55), but in comparison, associated only weakly with relapses in patients who presented with nonrenal disease (HR, 2.79; 95% CI, 1.30 to 5.98). From these studies, we conclude that longitudinal ANCA measurements may be useful in patients with renal involvement but is less valuable in patients with nonrenal disease. Whether measuring ANCA levels is useful to guide therapy in ANCA vasculitis will be discussed

## S15-4

### Multicenter studies for antineutrophil cytoplasmic antibody associated vasculitis in Japan

Ken-ei Sada<sup>1,2</sup>

<sup>1</sup>Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, <sup>2</sup>Research Committee on Intractable Vasculitides, the Ministry of Health, Labour, Welfare of Japan

Conflict of interest: None

In previous international collaborative studies, significant differences

in types of antineutrophil cytoplasmic antibody (ANCA) and disease classification have been recognized between western countries and Japan. To reveal efficacy and safety of treatments for ANCA-associated vasculitis (AAV) in Japan, several clinical studies have been conducted by the Research Committee on Intractable Vasculitides, supported by the Ministry of Health, Labour and Welfare of Japan. In 2004, severity-based treatment for Japanese patients with myeloperoxidase (MPO)-AAV (JMAAV) was started. Subsequently, a nationwide prospective cohort study in Japanese patients with all types of AAV (RemIT-JAV) performed from 2009 to 2013 and prospective study of patients with AAV and rapidly progressive glomerulonephritis (RemIT-JAV-RPGN) is underway since 2011. As for remission maintenance for AAV, extended study of RemIT-JAV and RemIT-JAV-RPGN are also ongoing (Co-RemIT-JAV and Co-RemIT-JAV-RPGN). Predominance of MPO-ANCA positive Japanese patients with AAV is confirmed even if in those with granulomatosis with polyangiitis (Wegener's) (GPA) in RemIT-JAV. In addition, it is also revealed that interstitial lung disease was an important clinical manifestation, and concomitant use of cyclophosphamide was less common and tapering speed of glucocorticoids was slow in the clinical setting in Japan. As for eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA), we performed a cross-sectional nationwide survey. We reported that 1,866 patients have EGPA in Japan and half of patients was MPO-ANCA positive. In contrast these similarity to western reports, female dominance and high prevalence of peripheral neuropathy were characteristic manifestations in Japan. We may have to reflect evidence based on western reports to our clinical practice in considering these characteristic manifestations of Japanese patients with AAV.

### S15-5

#### Emerging therapies for ANCA-associated vasculitis

Yoshinori Komagata

First Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

Conflict of interest: None

Standard therapy for ANCA-associated vasculitis has consisted of high-dose corticosteroids and immunosuppressant such as cyclophosphamide (CY) or azathioprine (AZA), even in remission induction or remission maintenance. Recently, it has been reported that anti-CD20 antibody, Rituximab (RTX), is as effective as CY is. RAVE trial mainly registered in USA showed similar remission induction rates for newly diagnosed patients between RTX and oral CY when combined with steroid pulse therapy. RITUXIVAS trial mainly registered in Europe also showed non-inferiority of RTX to IVCY for remission induction rate combined with 1mg/kg PSL, although RTX therapy showed high relapse rate. In Japan, RiCRAV trial by research groups of Ministry of Health, Labor and Welfare (MHLW) showed high remission induction rate and also high relapse rate. New randomized trial (RITAZAREM trial) evaluating efficacy and safety of periodical infusion of RTX as maintenance therapy is now ongoing. In this trial, relapsing patients of AAV after remission induction by CY or RTX are recruited. Several Japanese facilities have participated in the trial. RTX therapy for GPA and MPA was officially approved in Japan in June, 2013. However, in view of insufficient experiences of RTX use in Japan, Japan College of Rheumatology, Japanese Society of Nephrology, and research groups of MHLW made a statement for proper use of RTX at the same time. RTX therapy will be most important therapy for AAV for the next several years. Other emerging therapies that efficacy has been shown in clinical trials include CCX168, C5a receptor inhibitor, anti-BAFF antibody (Belimumab), anti-CD52 antibody (Alemtuzumab) that deplete lymphocytes and macrophages, and anti-IL-5 antibody (Mepolizumab) for EGPA. These new therapies will be discussed in this session.

### S16-1

#### Involvement of metabolic signals in immune regulation and diseases

Atsushi Kumanogoh

Graduate School of Medicine, Osaka University, Osaka, Japan

Conflict of interest: Yes

Immunometabolism, which integrates immunology and metabolism,

is an emerging research field. Nutrient derivatives (such as retinoic acid or oxysterols) and amino acid transporters are involved in activation/differentiation of lymphocytes and macrophages. In last years, intracellular nutrition sensor mTORC1 is also implicated in the activation/differentiation of immune cells. Furthermore, immuno-metabolic interaction is involved in the pathogenesis of common chronic diseases: Fatty acids induce activation of macrophages and chronic inflammation in obese patients with type 2 diabetes; Lactate is implicated in the induction of tumor-associated macrophages in cancer patients. Besides semaphorins, we have investigated the role of amino acid sensing molecules (Lamtor1, v-ATPase, and mTOR) in immune cells. Lamtor1 co-localizes at lysosome with v-ATPase, and is the scaffold for amino acid-activated mTOR. Among immune cells, Lamtor1 is expressed most abundantly in macrophages (MFs). When activated as M1MF, Lamtor1-null MFs produced larger amount of pro-inflammatory cytokines, but little IL-10. LPS challenge to Myeloid-specific Lamtor1 conditional KO mice resulted in drastic hypercytokinemia and septic death. M2 polarization was lost in Lamtor1-null MFs both *in vitro* and *in vivo*. We also investigated the role of Lamtor1 in regulatory T cells (Tregs). Treg-specific Lamtor1 conditional KO mice died by three weeks after birth, showing massive infiltration of immune cells in peripheral organs. We are investigating the function and signals in Lamtor1-null Tregs. Collectively, Lamtor1 was implicated in the regulation of inflammation and autoimmunity. It is intriguing that the physiological nutrition signal is coupled to the regulation of immune systems. Here I will discuss the mechanism, including the pathological implications of metabolic signals in autoimmunity.

### S16-2

#### Plasticity of Foxp3+T cells in autoimmune arthritis

Noriko Komatsu

Department of Immunology, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo

Conflict of interest: None

Autoimmune diseases often result from an imbalance between regulatory T (Treg) cells and interleukin-17 (IL-17)-producing T helper (TH17) cells; the origin of the latter cells remains largely unknown. Foxp3 is indispensable for the suppressive function of Treg cells, but the stability of Foxp3 has been under debate. Here we show that TH17 cells originating from Foxp3 (+) T cells have a key role in the pathogenesis of autoimmune arthritis. Under arthritic conditions, CD25 (lo)Foxp3 (+) CD4 (+) T cells lose Foxp3 expression (herein called exFoxp3 cells) and undergo transdifferentiation into TH17 cells. Fate mapping analysis showed that IL-17-expressing exFoxp3 T (exFoxp3 TH17) cells accumulated in inflamed joints. The conversion of Foxp3 (+)CD4 (+) T cells to TH17 cells was mediated by synovial fibroblast-derived IL-6. These exFoxp3 TH17 cells were more potent osteoclastogenic T cells than were naive CD4 (+) T cell-derived TH17 cells. Notably, exFoxp3 TH17 cells were characterized by the expression of Sox4, CCR6, CCL20, IL-23R and RANKL (also called TNFSF11). Adoptive transfer of autoreactive, antigen-experienced CD25 (lo)Foxp3 (+)CD4 (+) T cells into mice followed by secondary immunization with collagen accelerated the onset and increased the severity of arthritis and was associated with the loss of Foxp3 expression in the majority of transferred T cells. We observed IL-17 (+)Foxp3 (+) T cells in the synovium of subjects with active rheumatoid arthritis (RA), which suggests that plastic Foxp3 (+) T cells contribute to the pathogenesis of RA. These findings establish the pathological importance of Foxp3 instability in the generation of pathogenic TH17 cells in autoimmunity. Here, I would like to introduce the recent progress in the studies of bone destruction in autoimmune arthritis.

### S16-3

#### The role of T follicular helper cells in autoimmune diseases

Shingo Nakayama, Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health

Conflict of interest: None

T helper cells play critical roles for host defense and autoimmune diseases by their ability to differentiate into specialized subsets such as



Th1, Th2, Th17, and T follicular helper (Tfh) cells. Following the recognition of new subsets, there is increased recognition of plasticity and diversity in T helper subsets. In fact, T helper cells can express more than one master regulator. We identified the genome-wide mapping of histone epigenetic modifications in Tfh cells and reported that elements of plasticity in master regulators genes existed within the same subset. Tfh cells are critical for the formation and function of B cell responses, but also play an important role in autoimmunity. As circulating Tfh cells are reported to increase and correlates with disease activity in autoimmune diseases, our data confirmed that Tfh cells may play an important role in not only promoting autoantibody production but shaping the effector response to auto-reactive lymphocytes. For example, we found that flexible T-bet<sup>+</sup> Bcl6<sup>+</sup> Th1/Tfh like cells characteristically increased and might be involved in the pathogenesis of SLE. Moreover, effector cytokines produced by Tfh cells such as IFN- $\gamma$  induce pathological effector B cells, which lose CXCR5 and express CXCR3, resulting in the persistent pathogenic autoantibody production in patients with SLE. Thus, better understanding of the extrinsic and intrinsic signals that control epigenetic regulation and plasticity of Tfh cells will have important therapeutic applications to control autoimmunity.

### S16-4

#### B cell regulation by TGF-beta family molecules

Keishi Fujio, Tomohisa Okamura, Mariko Inoue, Kaoru Morita, Toshihiko Komai, Yukiko Iwasaki, Shinichiro Nakachi, Shuji Sumitomo, Kazuhiko Yamamoto

Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo

Conflict of interest: Yes

Tolerance inducing mechanisms for systemic autoimmune diseases have not been elucidated. In particular, understanding of physiological regulatory mechanisms for autoreactive B cells is important to develop a novel therapeutic strategy. Among various cytokines, TGF-beta1 is a unique cytokine that clearly inhibits B cell functions. TGF-beta1-deficient mice develop a systemic inflammatory disease with anti-RNP and anti-Sm antibodies. The putative source of TGF-beta1 is CD4+CD25+Foxp3+ regulatory T cells (CD25Treg), however, the disease phenotype of Foxp3-mutated IPEX patients is quite different from that of SLE. Previously, we identified a CD4+CD25-Foxp3- regulatory T cells (Treg) population that expresses both lymphocyte activation gene-3 (LAG3) and early growth response gene-2 (Egr2). We revealed that CD4+CD25-LAG3+ Treg (LAG3Treg) suppress antibody production in vivo and exhibit therapeutic activity in lupus-prone MRL/lpr mice in a TGF-beta3-dependent manner. In vitro, TGF-beta3 inhibits B cell proliferation and antibody production via the suppression of the phosphorylation of Syk, NF-kB, and STAT6. Moreover, TGF-beta3 cooperates with co-inhibitory molecule PD-1 in the control of B cells. Although CD25Treg produce moderate amount of TGF-beta1, TGF-beta3 produced by LAG3Treg may be a major source of TGF-beta activity from CD4+ T cells. Currently, the functional difference between TGF-beta3 and TGF-beta1 is under investigation. Further examination of LAG3Treg and TGF-beta3 may reveal the mechanisms for systemic autoimmunity.

### S16-5

#### Gut controls autoimmunity

Sachiko Miyake

Juntendo University School of Medicine

Conflict of interest: Yes

Autoimmune diseases are influenced by genetic and environmental factors. The intestine has lately received much attention as a potential location for the regulation of immune cells. We and other groups previously demonstrated that alterations of gut environment could lead to the amelioration of rodent model for autoimmune diseases. Recent studies demonstrated that particular bacteria could regulate immune responses. For example, segmented filamentous bacteria has been reported to exacerbate the autoimmune pathology in rodent models of autoimmune diseases in association of induction of Th17 cell. In contrast, Clostridium groups has been demonstrated to reduce colitis by inducing regulatory T cells. In this

session, we will present the data that gut is an important place to regulate autoantigen reactive T cells using TCR transgenic mice. In addition, we present the analysis data of human microbiota in patients with autoimmune diseases in comparison with in healthy volunteers. These studies may provide the novel strategy to prevent the development of autoimmune diseases as well as their disease progression.

### S17-1

#### New Classification Criteria for Idiopathic Inflammatory Myopathies

Ingrid E Lundberg<sup>1</sup>, Anna Tjärnlund<sup>1</sup>, Matteo Bottai<sup>2</sup>, Victoria P Werth<sup>3</sup>, Clarissa Pilkington<sup>4</sup>, Marianne de Visser<sup>5</sup>, Lars Alfredsson<sup>2</sup>, Anthony A Amato<sup>6</sup>, Richard J Barohn<sup>7</sup>, Matthew H Liang<sup>8</sup>, Jasvinder A Singh<sup>9</sup>, Frederick W Miller<sup>10</sup>, Lisa G Rider<sup>10</sup>

<sup>1</sup>Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden, <sup>2</sup>Institute for Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, <sup>3</sup>Department of Dermatology, Philadelphia VAMC and Hospital of the University of Pennsylvania, Philadelphia, USA, <sup>4</sup>Department of Rheumatology, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, <sup>5</sup>Department of Neurology, Academic Medical Centre, Amsterdam, Netherlands, <sup>6</sup>Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, USA, <sup>7</sup>Department of Neurology, University of Kansas Medical Center, Kansas City, USA, <sup>8</sup>Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, USA, <sup>9</sup>University of Alabama and VA Medical Center, Birmingham, USA, <sup>10</sup>Environmental Autoimmunity Group, Program of Clinical Research, National Institute of Environmental Health Sciences, National Institutes of Health, US Department of Health and Human Services, Bethesda, USA

Conflict of interest: None

**Background** An international, multidisciplinary collaboration, the International Myositis Classification Criteria Project (IMCCP), with support from ACR and EULAR, was established with the aim to develop and validate new classification criteria for adult and juvenile IIM and its major subgroups. **Methods** Candidate criteria variables were assembled from published criteria and inclusion criteria in controlled trials of myositis. Comparator groups confused with IIM were defined. Clinical and laboratory data from IIM and comparator patients were collected from 47 rheumatology, dermatology, neurology and pediatrics clinics worldwide from 2008-2011. Pair-wise associations among all items and between each item and clinicians' diagnoses were assessed. Explored approaches for derivation of classification criteria were: Traditional: case defined by specified number of items from a set Probability score: patient assigned a probability by summing score-points associated with the items Classification tree: case defined by a decision tree Internal validation using bootstrap methods and external validation using data from the Euro-myositis register and the Juvenile dermatomyositis cohort biomarker study and repository UK and Ireland was performed. **Results** Data from 976 IIM (73% adults; 27% children) (63% Caucasian; 18% Asian) patients and 624 comparators (82% adults; 18% children) (58% Caucasian; 25% Asian) were obtained. Comparators include other myopathies and rheumatic diseases. The new criteria comprise clinical items on muscles, skin, and laboratory measures, with the possibility to include muscle biopsy features (table). Each item has a score and the summed score corresponds to a probability of having IIM. Further sub-classification can be made using a classification tree. The criteria perform equally to, or better, than current published criteria. Each probability has specific sensitivity/specificity measures making it possible to use individual inclusion criteria for clinical studies. A minimum probability cutoff of 50% is mandatory and for clinical trials 90% probability is recommended for inclusion criteria. External validation using data on 592 adult or 332 juvenile IIM patients yielded 100% sensitivity. A web calculator was designed to facilitate calculations. **Conclusion** The new classification criteria for IIM have easy-to-access items and generally superior performance compared to existing criteria.

### S17-2

#### New findings of anti-aminoacyl-tRNA synthetase antibody syndrome

Hajime Yoshifuji

Department of Rheumatology and Clinical Immunology, Graduate

Conflict of interest: None

Idiopathic inflammatory myopathy (IIM) is considered a group consisted of heterogeneous subgroups. Various autoantibodies are found in IIM and useful because they correlate with clinical features of IIM (Love, Medicine, 1991). Eight kinds of anti-aminoacyl-tRNA synthetase (anti-ARS) antibodies have been found in IIM. Anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS, anti-Ha, and anti-Zo antibodies recognize histidyl, threonyl, alanyl, glycyl, isoleucyl, asparaginy, tyrosyl, and phenylalanyl tRNA synthetases, respectively. Clinical features such as interstitial lung disease (ILD), polyarthritis, and mechanic's hands are common among patient positive for all kinds of anti-ARS antibodies; it implies the association between autoantibodies and pathophysiology of IIM. ILD complicated with anti-ARS-positive IIM responds well to glucocorticoids (GC), but these ILD easily recurs (Yoshifuji, Autoimmunity, 2006). Now, we stratified 104 anti-ARS-positive IIM patients with ILD into 3 groups: (I) who received immunosuppressants (IS) in the 1st year after the initial GC, (II) who received IS 1 or more years after the initial GC, and (III) who received GC without IS. Survival rates were best in group I and worst in group III, suggesting that initial combination of GC and IS will be advantageous to treat ILD complicated with anti-ARS-positive IIM. For long, only anti-Jo-1 antibody was available commercially. Recently, a new ELISA system (Nakashima, PLoS One, 2014) for 5 kinds of anti-ARS-antibodies was approved in Japan, and it will be useful for the diagnosis and treatment selection of IIM. There have been several reports that give us sights to consider the pathogenesis of IIM: (1) association between genetic backgrounds and anti-ARS antibodies, (2) evidence that there are abundant expression of histidyl-tRNA synthetase in regenerating muscle fibers in IIM, and (3) mimicry between tRNA of eukaryotes and RNA of picornavirus.

### S17-3

#### Novel autoantibodies in idiopathic inflammatory myopathy

Manabu Fujimoto

Department of Dermatology, Faculty of Medicine, University of Tsukuba

Conflict of interest: None

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of acquired skeletal muscle diseases that include polymyositis, dermatomyositis, and inclusion body myositis, affecting both adults and children. Studies have shown that a variety of autoantibodies, directed against cytoplasmic or nuclear components, can now be identified in patients with IIMs. They are useful for the diagnoses as well as classification of IIMs, because they have been shown to correlate with distinct clinical phenotypes. In addition to well-know autoantibodies including anti-Jo-1 and other anti-aminoacyl tRNA synthetase antibodies and anti-Mi-2 antibody, autoantibodies described recently include anti-melanoma differentiation antigen 5 (MDA5) antibody (also called as anti-CADM140 antibody), anti-transcription intermediary factor 1 (TIF1) antibody (also called as anti-155/140 and anti-p155), anti-nuclear matrix protein 2 (NXP-2) antibody (also called as anti-MJ antibody), and anti-small ubiquitin like modifier activating enzyme (SAE) antibody. Anti-MDA5 antibody is clinically associated with amyopathic dermatomyositis developing into rapidly progressive interstitial lung disease, whereas anti-TIF1 and anti-NXP-2 antibodies are closely correlated with cancer-associated dermatomyositis in adults. Anti-TIF1 and anti-NXP-2 antibodies are also predominant MSAs found in juvenile dermatomyositis, and the latter was correlated with a high incidence of calcinosis. Furthermore, anti-signal recognition particle (SRP) antibody has been identified to be associated with necrotizing myopathy. An update of new emerging insights about the clinical significance of these autoantibodies, especially anti-TIF1 and anti-NXP-2 antibodies, will be provided.

### S17-4

#### Histopathological and nEMG findings of idiopathic inflammatory myopathies

Jun Shimizu

Department of Neurology, University of Tokyo, Graduate School of Medicine

Conflict of interest: None

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of systemic autoimmune disorders characterized by proximal and symmetric muscle weakness and skeletal muscle inflammation. From histopathological viewpoints, IIMs are classified into four subsets: polymyositis (PM), dermatomyositis (DM), necrotizing autoimmune myositis (NAM) and nonspecific myositis (NSM). As the common pathological findings of all subsets, variable amounts of necrotic or regenerating muscle fibers, variable amounts of inflammatory exudates in muscle, and increased expression of MHC class I antigen in non-necrotic muscle fibers are usually observed. In addition to the common pathological findings, the findings that characterize each subset are as follows: infiltration of CD8+ T-cells surrounding and invading non-necrotic muscle fibers in PM, deposition of the C5b-9 complement on small blood vessels or per fascicular atrophy in DM, and presence of many necrotic muscle fibers with sparse inflammatory cells in NAM. Although the characteristic findings for PM, DM or NAM are considered to be important in pathological mechanisms, the percentages of the patients with these findings are not always high. In clinical practice, many patients with IIMs showing non-specific muscle pathological changes (NSM), are encountered. In patients with IIMs, examination by needle electromyography (nEMG) is essential for the correct diagnosis of IIMs. Typically, nEMG in patients with IIMs shows spontaneous activity with myopathic changes. nEMG is important not only for the diagnosis of myositis but also for the selection of the muscle for pathological examination. nEMG is also helpful in the differentiation of steroid-induced myopathy from a relapse of myositis in patients with relapsing weakness during steroid therapy.

### S17-5

#### Update on the Treatment of Idiopathic Inflammatory Myopathies

Yasuhiro Katsumata

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

Recently published expert opinions on treatment of polymyositis (PM) and dermatomyositis (DM) were systematically searched via PubMed. There were 5 papers that reviewed the treatment strategy of PM/DM. Schmidt *et al.* use pulsed intravenous glucocorticosteroids (GCs) and subsequent prednisone at 1 mg/kg/day for 6-8 weeks. Simultaneously with GC, they start azathioprine (AZA), methotrexate (MTX), or mycophenolate mofetil (MMF) with this order of priority. If treatment with any of these drugs alone remains ineffective, they additionally administer intravenous immunoglobulin (IVIg). Options for treatment escalation include rituximab, cyclophosphamide (CY), or cyclosporine (CS). Reed *et al.* initiated prednisone at 0.5-1 mg/kg/day (60-80 mg/day), with a taper after 2-4 weeks. Concurrent with GCs, they administer AZA, MTX or MMF. In severe or refractory cases, they use pulsed intravenous methylprednisolone, IVIg, CY, rituximab, or CS with this order of priority. Marie *et al.* prescribe oral prednisone at 1mg/kg/day as the first-line of therapy for at least 4-8 weeks, and then the daily dose of prednisone can be tapered. In patients who failed to respond to prednisone alone, the first-line immunosuppressive therapy comprises MTX or AZA with this order of priority. IVIg therapy is considered in patients in whom those cytotoxic drugs are contra-indicated. In patients who fail to respond to this therapeutic strategy, a number of therapeutic agents may be proposed, including MMF and rituximab. Lundberg *et al.* suggested using prednisone at 0.75-1 mg/kg/day for several weeks simultaneously with MTX or AZA. They recommended CS or MMF as second-line agents. Oddis *et al.* suggested using initial treatment with prednisone at a dosage of 1 mg/kg/day (60-80 mg/day) combined with AZA or MTX to facilitate subsequent tapering of prednisone. In refractory cases, IVIg can be tried, followed by CS or tacrolimus in patients possessing antisynthetase autoantibodies, or MMF in refractory skin disease.

### S17-6

#### Human induced pluripotent stem cell-derived myocytes mimic myoblasts in producing cytokines that may exacerbate myositis

Hisanori Hasegawa<sup>1</sup>, Kimito Kawahata<sup>1</sup>, Haruna Takagi<sup>2</sup>, Makoto Otsu<sup>2</sup>, Hitoshi Kohsaka<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), Tokyo, Japan, <sup>2</sup>Stem Cell Bank & Division of Stem Cell Processing, Center for Stem Cell Biology and Regenerative Medicine, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

Conflict of interest: None

A series of studies on a model of polymyositis (PM) have revealed that activation of autoreactive T cells and of innate immunity in the muscle tissues are crucial for development of autoimmune myositis. Furthermore, we elucidated that injury and subsequent regeneration of muscles activate innate immunity to facilitate development of myositis. Differentiating myocytes during muscle regeneration produced inflammatory cytokines. Genetic properties of myocytes to produce cytokines in PM/dermatomyositis (DM) patients may facilitate development of myositis. It was reported that human induced pluripotent stem cells (hiPSCs) overexpressing a myogenic transcription factor, MyoD, differentiated into spindle-like myocytes with expression of myogenic markers. If we can induce hiPSCs derived from healthy controls and from PM/DM patients to differentiate into myocytes, we will be able to verify the differences of genetic properties in cytokine production. In addition, we can assess the feasibility of hiPSC transplantation to PM/DM patients. We generated 2 clones of healthy control-derived hiPSCs with doxycycline (Dox)-inducible MyoD expression (MyoD-hiPSCs). When cultured in differentiation media with Dox, MyoD-hiPSCs differentiated into myocyte-like spindle cells and produced CCL2, which was detected with ELISA. Without the Dox treatment, MyoD-hiPSCs did not produce CCL2. There were no variation between 2 MyoD-hiPSC clones in the morphological changes and CCL2 production. While undifferentiated MyoD-hiPSCs in hiPSC maintenance media produced CCL2, CCL2 production increased during myogenic differentiation. We will compare the quantity and variety of cytokines produced from healthy control- and PM/DM patient-derived MyoD-hiPSCs differentiating into myocytes. Since hiPSC-derived myocytes can produce a proinflammatory cytokine, transplantation of hiPSC-derived myocytes to PM/DM patients may exacerbate myositis. This should be circumvented in applying hiPSC transplantation.

### S17-7

#### The front line in treatment of interstitial lung disease associated with polymyositis/dermatomyositis

Shinji Sato

Division of Rheumatology, Department of Internal Medicine, Tokai University, School of Medicine, Isehara, Japan

Conflict of interest: None

Polymyositis/Dermatomyositis (PM/DM) is often accompanied by interstitial lung disease (ILD) that is one of prognostic factors of this condition. Clinical courses, response to therapy and prognosis of ILD are heterogeneous in each case. There are mainly two types of ILD in terms of their clinical course, chronic type and acute/ sub-acute type. Chronic ILD is a type of non-progressive or slowly progressive in a long period and histopathological findings indicate non-specific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP). Although it has been believed that prednisolone mono therapy was effective to this condition, combination use of immunosuppressant is recommended because of high frequency of relapse during the dose reduction of PSL. Acute/ sub-acute type that indicates diffuse alveolar damage (DAD) histopathologically is often resistant to intensive therapy (high-dose corticosteroid with more than one immunosuppressant) and results in an undesirable outcome. This type of ILD is mainly found in patients with clinically amyopathic dermatomyositis (CADM), a clinical subtype of DM especially these patients from East Asia. Since effective treatment for this condition has not been established, early intensive therapy before development of severe respiratory failure has been emphasized so far. On the other hand, acute/ sub-acute type that shows COP histopathologically has good response to treatment and favorable outcome.

### S18-1

#### A fundamental knowledge of the pain for the rheumatologists

Natsu Koyama

Shiga University of Medical Science

Conflict of interest: None

Many case of the pain, which perceived an unpleasant sensory and emotional experience, acts as a warning system that protect the body from the dangerous environment. Children with congenital insensitivity to pain usually have many damaged or missing tissues, because they cannot learn how to avoid injury. Pain is always subjective, and individual differences in pain perception may be big although the severity of injury appears similar. Even in the same person, degree of pain may not be always constant. Generally, noxious stimulus activated the sensory receptors are transduced to electric signals, which are ultimately transmitted to the pain-related brain areas includes somatosensory and limbic cortical regions, where conscious pain is generated. Nociceptors are the specialized sensory receptors responsible for the detection of noxious stimuli, including nociceptive thermal or mechanical stimuli as well as environmental and endogenous chemical irritants. But the noxious stimuli for the skin are not always activate the nociceptor of other tissues. Noxious stimuli do not evoke pain in all situations, and innocuous stimuli can evoke pain in some situations. Moreover, there is the pain without activation of nociceptor. Inflammation or nerve injury gives rise to changes in sensory processing at peripheral and central nociceptive neurons with a resultant sensitization. Once sensitization has occurred, stimuli which normally would not produce pain are perceived as painful (allodynia) and there is an exaggerated response to painful stimuli (hyperalgesia). Peripheral sensitization more commonly results from inflammation-associated changes in peripheral terminal, altering gene expression in soma on the dorsal root ganglion. Mechanisms of central sensitization include glutamatergic NMDA receptor-mediated hypersensitivity, loss of tonic inhibitory controls and glial-neuronal interactions. Not only negative emotion but also positive emotion modulates the pain cognition.

### S18-2

#### Establishment of painful dysesthesia animal models and its mechanisms

Takayuki Nakagawa<sup>1,2</sup>

<sup>1</sup>Department of Clinical Pharmacology and Therapeutics, Kyoto University Hospital, Kyoto, Japan, <sup>2</sup>Department of Molecular Pharmacology, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan

Conflict of interest: None

Dysesthesia is an unpleasant abnormal sensation such as tingling, pricking and pins-and-needles, sometimes accompanied with pain, paresthesia and numbness. Dysesthesia is associated with various diseases such as diabetic neuropathy, entrapment neuropathy, arterial occlusive disease and chemotherapy-induced peripheral neuropathy. However, the mechanisms are largely unknown because of the lack of animal model. First, we focus that oxaliplatin, a platinum-based agent, causes peculiar acute peripheral neuropathy including dysesthesia, which appear in almost all patients during or within hours after infusion, and is triggered or exacerbated by cold. We found that oxaliplatin or its metabolite oxalate induced cold hypersensitivity within 2 h in mice, which is mediated through a nociceptor TRPA1 expressed in primary sensory neurons. Furthermore, we found that oxaliplatin could sensitize TRPA1 function via dehydroxylation of proline 394 in TRPA1 N-terminal by inhibition of the enzymatic activity of oxygen-sensitive proline hydroxylase, and the sensitized TRPA1 is activated by reactive oxygen species (ROS). On the other hand, we often experience that dysesthesia is evoked after ischemia and reperfusion of upper or lower limb. Second, we tried to establish a mouse dysesthesia model induced by transient hindlimb ischemia/reperfusion. We tightly ligated a hindlimb of mouse for 1 h, and then removed the ligation. Hypoesthesia to tactile stimuli was evoked during ischemia and after reperfusion. After the reperfusion, spontaneous licking to the hindlimb was evoked, which peaked within 10 min. Furthermore, we found that the transient ischemia/reperfusion-evoked spontaneous licking is mediated through TRPA1 activated by post-ischemic ROS production. These results suggest that an aspect of dysesthesia, *i.e.* painful dysesthesia, is caused by the sensitization of redox-sensitive TRPA1 through dehydroxylation of a proline residue and subsequent activation of TRPA1 by ROS.

### S18-3

#### The chronic pain in rheumatoid arthritis considered by orthopedist

Hiroki Yajima<sup>1</sup>, Tatsuo Watanabe<sup>2</sup>, Toshihisa Kojima<sup>2</sup>, Naoki Ishiguro<sup>2</sup>  
<sup>1</sup>Department of Orthopedic Surgery, Nagoya Ekisaikai Hospital, <sup>2</sup>Department of Orthopedic Surgery, Nagoya University School of Medicine

Conflict of interest: None

There are the intractable chronic pain and the prolonged acute pain in the rheumatoid arthritis. Classifying by mechanism, the inflammatory pain by rheumatic inflammation, the nociceptive pain by mechanical stimulation of osteoarthritis, the neuropathic pain by spondylosis or peripheral nerve entrapment. Also the chronic pain caused by long-term pain stimulation is included. It is difficult to distinguish it definitely, and these are often mixed. Watanabe et al reported last year that HAQ-DI related to patient VAS. Lower patient VAS improves not only the functional disorder but also the disease control. The purpose of treatment is to suppress inflammation and joint destruction, also it is important to relieve pain. Lowering disease activity by DMARDs and steroid administration make suppressing the inflammatory pain. For the nociceptive pain due to the arthropathy, conservative medical treatment such as NSAIDs, rehabilitation and brace are used. If the effect is insufficient, perform surgical managements such as the joint arthroplasty. The effect of pain relief by the joint arthroplasty is superior. The recommendation degree of knee joint and hip joint is high, although lower of shoulder, elbow and ankle because of high rate of complications. Pregabalin administered for neuropathic pain. The neurolysis and the decompression performed for serious case. Medication is used for the failure case. Usually NSAIDs is given, but opioid for the case such as a long term use, kidney dysfunction. Pregabalin is often effective for neuropathic pain. The additional therapeutic exercise is important. For the chronic pain that a mental factor is included in, treatment from many aspects in cooperation with psychiatry and psychosomatic medicine is needed.

### S18-4

#### Chronic pain patients from a psychiatric viewpoint

Noriyuki Hayashi  
Department of Integrative Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

Conflict of interest: Yes

ICD-10 defines persistent somatoform pain disorder as “persistent (at least six months, continuously on most days) severe and distressing pain, in any part of the body, which cannot be explained adequately by evidence of a physiological process or a physical disorder, and which is consistently the main focus of the patient’s attention”. It is a big problem that distressing pain is consistently the main focus of the patient’s attention. A true problem in a chronic pain is not painful but consistently the main focus of the patient’s attention on pain and they cannot anything. Most of them think “Nothing will be done to feel this pain” and try in order to get this pain off first. It called catastrophic thought. At that time, we try cognitive behavioral therapy (CBT). CBT have three approaches which are cognitive, behavioral, and mindfulness. We use those approaches appropriately according to the patients. It’s important these intervention is training and we should train ourselves daily as a trainer.

### S18-5

#### Psychosomatic Orthopedics

Hirota Tanikawa  
Tanikawa Orthopaedic Clinic

Conflict of interest: None

Psychological evaluation should ideally be performed across all clinical departments. The author emphasizes that reason, and appropriate if there is a position that psychosomatic orthopedic. Several conditions such as neck stiffness and low back pain cause pain in locomotive organs. In recent times, the proportion of elderly patients with pain in the limbs and trunk due to musculoskeletal degenerative diseases such as arthrosis and spondylosis has increased dramatically. According to the guidelines for low back pain, 85% of all low back pain is of unknown etiology

meaning shocking result that there has been specified. However, orthopedic surgeons have commonly observed that, most patients with back pain are typically unable to determine the cause of the pain. This is probably because the physical causative factor of most musculoskeletal pain is often minor. Patients with psychological involvement are usually convinced that their discomfort condition is not psychosomatic, but stems rather from somatic disorders. As the physician–patient relationship is very important, orthopedic practitioners should be particularly alert and sensitive in supporting patients who exhibit both possible psychosomatic disorders and locomotive organ symptoms, because these patients expect the doctor to treat them as having only a somatic disease, and not a psychological one. While it is possible that the locomotive organ may be located at the opposite side of the psychology, the orthopedic practitioner should establish a good relationship with patients having psychosomatic disease, without expressing blatant suspicion of psychological involvement. Thus, I conclude that physical treatment by orthopedic practitioners might be an adequate psychosomatic approach for patients with locomotive organ pain.

### S18-6

#### Pain among persons with physical impairments and neurodevelopmental disorders

Shinichiro Kumagaya  
Research Center for Advanced Sciences and Technology, The University of Tokyo

Conflict of interest: None

It has been reported that persons with physical impairments like cerebral palsy tend to have chronic pain. In recent years, among people with autism spectrum disorders, which is one of the neurodevelopmental disorders, atypical processing patterns of nociceptive inputs and prolonged lingering pain are also reported. In this talk, I propose the hypothesis that pain could be regarded as collapse of self-representation, based on the previous studies of pain science.

## International Symposium

### IS1-1

#### Novel Approaches for the Treatment of Osteoporosis

Roland Baron

Harvard Medical School, Endocrine Unit, Massachusetts General Hospital, Boston, USA

Conflict of interest: Yes

Osteoporosis is the result of a dysfunction of the bone remodeling process where an imbalance between bone resorption and bone formation leads to loss of bone mass, altered microstructure and fragility fractures. Novel therapeutic approaches have not only provided better treatment modalities but also shed new light on the mechanisms by which skeletal homeostasis, including trabecular and cortical bone, is regulated. Treatment of osteoporosis with anti-resorptives is associated with a decrease in remodeling activity, including bone formation, due to the osteoclast-osteoblast coupling process. Denosumab treatment nevertheless allows a continued increase in bone density over time. The mechanisms by which bone mass continues to increase despite very low remodeling activity remain elusive but may involve modeling activity. In contrast, inhibition of cathepsin K decreases bone resorption while maintaining bone formation, allowing cross-talk between osteoclasts and osteoblasts and a robust and prolonged increase in BMD at trabecular and cortical sites. Bone mass can also be efficiently increased by treatment with bone anabolics. Daily PTH injections increase bone formation but also bone resorption, increasing bone turnover, albeit with a positive balance. The secondary increase in bone resorption may however affect intracortical remodeling. Weekly administration of PTH, the use of PTHrP or the combination of PTH with denosumab may avoid in part the increase in resorption. The other new anabolic approach targets Wnt signaling. The novel anabolics are sclerostin antibodies that enhance locally, at the level of osteoblasts and osteocytes, Wnt signaling. These compounds appear to have an anabolic and anti-resorptive effect that, albeit limited in time, increases even more efficiently bone density at trabecular and cortical sites. Taken together, these new therapeutic developments provide promising prospects for the future treatment of osteoporosis.

### IS1-2

#### Osteoporosis treatment in Japan

Sakae Tanaka

Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Japan

Conflict of interest: Yes

Osteoporosis is a burden for aged societies such as Japan and USA, and increasing number of people are suffering from osteoporosis and osteoporotic fractures such as vertebral fractures and hip fractures in these countries. In Japan, it has been reported that the rate of hip fractures is still increasing. This is at least partly because the rate of medical treatment in osteoporosis patients is still very low, and only 10-20% of those who need treatment are properly treated. Japan Bone and Mineral Society/Japan osteoporosis society published a guideline for the Prevention and Treatment of Osteoporosis, and made a recommendation for osteoporosis treatment based on their effects on increasing bone mineral density and preventing fragility fractures. Bisphosphonates are one of the most successful anti-osteoporotic drugs, and accumulating clinical evidence has demonstrated the effectiveness of bisphosphonates to prevent osteoporotic fractures. Anti-RANKL antibody, denosumab, also reduces hip fracture incidence. In spite of such clinical success, several problems have been pointed out in the long-term use of bisphosphonates such as osteonecrosis of the jaw, atypical femoral fractures etc. For those who cannot be treated with first line drugs, we have some second line drugs including active vitamin D such as eldcalcitol and alfacalcidol. Eldcalcitol is an analog of calcitriol and possesses a hydroxypropoxy substituent at the 2b-position of calcitriol. Eldcalcitol treatment increases lumbar and hip bone mineral density in osteoporotic fractures by suppressing bone turnover, and reduced vertebral fracture incidence as compared with alfacalcidol in phase III fracture prevention trial. In addition to these anti-bone resorbing agents, a bone anabolic drug teriparatide has been approved in Japan in two different regimens; once a day and once a week

regimens. a daily 20 µg treatment regimen (relative risk reduction (RRR): 65%) and a once-weekly 56.5 µg treatment regimen.

### IS1-3

#### Anti-RANKL therapy

Takeshi Miyamoto

Keio University School of Medicine, Tokyo, Japan

Conflict of interest: Yes

Osteoporosis is defined by national Institutes of Health (NIH) as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. NIH also stated that bone strength reflects the integration of two main features: bone density and bone quality, and although, currently there is no accurate measure of overall bone strength, bone mineral density (BMD) is frequently used as a proxy measure and accounts for approximately 70 percent of bone strength. Thus, reduced BMD is considered major cause for osteoporosis development. Reduced bone mass seen in osteoporosis is mainly due to elevated osteoclast activity compared with osteoblasts, and that controlling osteoclasts is crucial to treat osteoporosis patients. In 1998, receptor activator of nuclear factor kappa B ligand (RANKL) was identified as an osteoclast differentiation factor, and RANKL-deficient mice were demonstrated exhibited complete lack of osteoclast formation with osteopetrotic phenotypes. Thus, RANKL was considered a promising therapeutic target to treat osteoporosis patients. Indeed, we and others found that RANKL transduces diverse signals for osteoclast differentiation. We also found that RANKL expression was activated in cynovium and sunchondral bones of joints in inflammatory arthritis models in an inflammatory cytokine mediated feedback mechanism via signal transducer and activator of transcription 3 (Stat3). RANKL was reportedly demonstrated as a target to prevent bone erosion in inflammatory arthritis model. Now, Denosumab, a neutralizing antibody against RANKL was launched to treat osteoporosis patients. I will discuss about recent findings on RANKL, and its pathogenic roles in osteoporosis and bone erosion in inflammatory arthritis.

### IS1-4

#### Effects of denosumab and alendronate on cortical and trabecular bone

Roger M Zebaze

Austin Health, University of Melbourne, Melbourne, Australia

Conflict of interest: Yes

Vertebral fractures and trabecular bone loss are hallmarks of osteoporosis. However, 80% of fractures are non-vertebral and 70% of all bone loss is cortical in older women. Bisphosphonates reduce non-vertebral fractures by only 20-30%, less than half their anti-vertebral fracture efficacy. Thus, reducing cortical bone fragility and non-vertebral fractures is an unmet challenge. Antiresorptives are the first treatment for osteoporosis. However, not all antiresorptives are similar. Bisphosphonates such as Alendronate binds primarily within superficially-located mineralised bone matrix such as trabecular surfaces, but may not be able to readily access deep intracortical surfaces where remodeling imbalance is responsible for most (~70%) of bone loss that occurs with advancing age. Denosumab on the other hands, a fully human anti-RANKL antibody, does not bind to bone matrix, and so is widely distributed and thus more readily accesses deep intracortical surfaces. It is proposed that this pharmacokinetic difference may result in differing effects of alendronate and Denosumab on cortical bone. The effects of both drugs on trabecular bone however may be more similar. There is evidence suggesting that Denosumab restores more cortical microarchitecture than alendronate partly because of its greater accessibility to remodeling throughout the skeleton. This presentation will discuss the available data and the implications for fracture prevention.

### IS1-5

#### Inhibition of Cathepsin K: A New Approach for the Treatment of Osteoporosis

Le T. Duong

Bone Biology, Merck Research Laboratories, West Point, Pennsylvania,

USA

Conflict of interest: Yes

An emerging target for the treatment of osteoporosis is cathepsin K, an osteoclast cysteine protease. This enzyme is primarily responsible for the degradation of proteins present in the organic matrix of bone including collagen type I. Odanacatib (ODN) is a selective and reversible cathepsin K inhibitor (CatKi). *In vitro* CatKi's reduce osteoclastic bone resorption efficiency without impairing osteoclastogenesis. Genetic and pharmacologic evidence has demonstrated that inhibition of CatK reduces bone resorption while allowing bone remodeling as determined by bone formation rate to continue in mice and ovariectomized (OVX) rabbits. ODN daily dosing in OVX-monkeys in prevention mode increased bone mineral density (BMD) of the spine, total hip and femoral neck. ODN reduced remodeling-based bone formation in the spine, while dose-dependently enhancing modeling-based bone formation in cortical surfaces of the hip, leading to significant increased cortical thickness, improved bone strength. In a phase 2 clinical trial extended over 5-years, postmenopausal women with osteoporosis (PMOP) receiving ODN 50mg once-weekly presented a sustained reduction of bone resorption markers, whereas procollagen type 1 N-terminal propeptide returned toward baseline. In turn areal BMD of spine and total hip increased continuously upto 5 years. The ODN phase III clinical trial included ~16,000 PMOP for 3 years, with 8000 of them in a 5-year extension with maintained randomization. ODN 50mg once-weekly demonstrated significant reduction of vertebral, non-vertebral and hip fractures. Several infrequent but numerically higher adverse events in patients on active therapy versus placebo are under further detailed investigations. Taken together, the CatKi ODN protects bone mass, reduces fracture risk at all sites via a molecular mechanism distinct from the standard antiresorptives

## IS2-1

### Monitor and modulate follicular helper T (T<sub>fh</sub>) cells in human autoimmune diseases

Di Yu

Laboratory for Molecular Immunomodulation, School of Biomedical Sciences, Monash University, Melbourne, Australia

Conflict of interest: None

Follicular B helper T (T<sub>fh</sub>) cell is a CD4 T cell subset specialised to regulate high-affinity and long-term antibody responses. The differentiation and function of T<sub>fh</sub> cells are regulated by a unique molecular program including transcriptional factors, such as Bcl6, co-stimulators, such as ICOS, signalling molecules, such as SAP and cytokines, such as IL-21. I will briefly review recent advance on the molecular mechanism for T<sub>fh</sub> cell differentiation and function, and then focus on the role of T<sub>fh</sub> cells in human autoimmune diseases. T<sub>fh</sub> cell support the production of autoantibodies and promote disease development and progress. Using animal models and human samples, early memory T<sub>fh</sub> cells in blood with a CXCR5<sup>+</sup>CCR7<sup>low</sup>PD-1<sup>high</sup> phenotype was characterised. The increase of the early memory T<sub>fh</sub> cells in blood represents the active T<sub>fh</sub> cell differentiation and correlates with the disease activities of systemic lupus erythematosus and rheumatoid arthritis. Using CXCR5<sup>+</sup>CCR7<sup>low</sup>PD-1<sup>high</sup> early memory T<sub>fh</sub> cells as a reliable marker, we demonstrate low-dose IL-2 can specifically suppress T<sub>fh</sub> function to treat systemic lupus erythematosus.

## IS2-2

### Pathological involvement of semaphorins and mitochondrial DNAs

Atsushi Kumanogoh, Yuji Yoshida, Toru Hirano, Hyota Takamatsu  
Graduate School of Medicine, Osaka University, Osaka, Japan

Conflict of interest: Yes

In this session, we will focus on two topics, that is, pathological implications of semaphorins and mitochondrial DNAs (mtDNAs) in collagen diseases. Semaphorins were originally identified as neural guidance factors. Accumulating evidence demonstrates that several semaphorins play important roles in various phases of immune responses and diseases. Among them, Sema4D/CD100 was the first semaphorin identified in the

immune system. Although Sema4D is a membrane-bound protein, it also exists as a functional soluble form (sSema4D) following proteolytic cleavage upon cellular activation. Of note, Sema4D derived from osteoclasts suppressed the bone formation by osteoblasts, of which blocking results in increased bone mass. However, the involvement of Sema4D in the pathogenesis of RA has not been determined yet. We here present that sSema4D levels were elevated in sera and synovial fluids from RA patients. The elevated levels of sSema4D were produced by an inflammation-related proteolytic mechanism and resulting sSema4D in turn induced inflammation, suggesting the existence of an autocrine inflammation loop in RA synovium. Inhibition of Sema4D ameliorated the symptoms of CIA. The results indicated that Sema4D represents a potential target for treatment of RA. In search for semaphorin-mediated signals, we found a signaling cascade related to the mitochondria metabolism and the elevations of mtDNAs in Behçet's disease (BD). Interestingly, mtDNAs were enveloped inside exosomes and released by monocytes. Additionally, BD-derived exosomes promoted sterile inflammation by enhancing neutrophil mobilization and cytokine production, in which Toll-like receptor 9 and NLR family, pyrin domain containing 3 inflammasome were crucial, suggesting the pathological implications of mtDNAs in BD. 1) Schults E et al. Nature Comm. 5:5191, 2014 2) Nojima S et al. Nature Commun. 4:1406, 2013. 3) Kumanogoh A and Kikutani H. Nature Rev Immunol. 13:802, 2013.

## IS2-3

### Immune Aging, Inflammation and Autoimmunity

Jorg J Goronzy<sup>1,2</sup>, Cornelia M Weyand<sup>1,2</sup>

<sup>1</sup>Division of Immunology and Rheumatology, Department of Medicine, Stanford University, Stanford, USA, <sup>2</sup>VAPAHCS, Palo Alto, USA

Conflict of interest: None

Aging is associated with a decline in immune competence, causing morbidity and mortality from infections, as well as an increased incidence of malignancies. Less intuitively, the aging immune system is also more inclined to elicit nonspecific inflammation accelerating degenerative diseases, most prominently seen in cardiovascular and neurodegenerative disorders. Even more strikingly, age is also a risk factor for several autoimmune diseases, including rheumatoid arthritis, polymyalgia rheumatica and giant cell arteritis. At first sight, co-occurrence of immune deficiency and autoimmune susceptibility appears to be contradictory. Age-associated changes in the adaptive immune system are most striking since the thymus involutes in young adults. Using next-generation sequencing of the T cell receptor repertoire, we showed that older individuals maintain a sufficiently diverse repertoire. However, both naïve and memory T cells develop defects in their signaling pathways that render them low-responsive. In a T cell-centered view, the increased inflammatory state therefore can be explained as failed adaptive immunity that is no longer able to prevent the reactivation of latent viruses leading to innate immune stimulation. Moreover, age is also associated with the accumulation of T effector cell populations that contribute to inflammatory responses. Both mechanisms, however, do not explain the increased propensity for autoimmunity. One alternative model, coming from the observation of lymphopenia-induced autoimmunity in mice, is that the old T cell repertoire is selected towards autoreactivity. Indeed, our repertoire analysis provided evidence that uneven homeostatic proliferation, driven by self-recognition and responses to homeostatic cytokines throughout life, is associated with large expansion of naïve T cell clones with possibly increased affinity to self. An increased risk for autoimmunity may be the price we have to pay to preserve immune function into older age.

## IS2-4

### Cytokine and autoantibody mediated bone loss- Implications for RA

Georg Schett

Department of Internal Medicine 3, University of Erlangen-Nuremberg, Germany

Conflict of interest: None

Inflammatory diseases lead to rapid degradation of bone, which translates to bone erosion, premature osteoporosis, increased fracture risk

and impaired growth in children, adolescents and adults affected by inflammatory diseases. Understanding the mechanisms of how immune activation impairs bone mass and quality are of seminal importance to prevent the negative consequences of diseases such as arthritis on the bone. Cytokines with well-established function in human inflammatory diseases, such as TNF $\alpha$ , IL-1 $\beta$  and IL-6 distort the balance between bone formation and bone resorption in favor of the latter one. Importantly, all these three principle pro-inflammatory cytokine facilitate the differentiation of bone resorbing osteoclasts from monocyte precursors, thereby inducing enhanced bone resorption. Aside inflammatory cytokines, immunoglobulins, in particular autoantibodies, may influence bone balance. For instance, antibodies against citrullinated proteins directly induce the generation of bone resorbing osteoclasts and induce bone loss. Rheumatoid arthritis is characterized by autoantibodies against citrullinated proteins, which have been posttranslationally modified by peptidyl-arginine deiminases (PAD) that convert arginine to citrulline. These antibodies are one of the strongest risk factors for bone destruction in rheumatoid arthritis and we have recently shown that even healthy individuals with such antibodies show signs of cortical bone loss. This latter finding indicates the autoimmunity can affect bone even without clinically apparent inflammatory disease. Hence, neutralization of inflammatory cytokines may represent only one strategy to inhibit inflammatory bone loss, whereas targeting autoimmunity may be an even better intervention strategy to disrupt the deleterious interaction between the immune system and bone. One strategy to influence the effects of autoantibodies on the bone may be the modulation of their glycosylation. Glycosylation of antibodies determines their binding to Fc-receptors. Osteoclast lineage cells bear Fc-receptors and recent data show that the osteoclastogenic potential of immunoglobulins depends on their glycosylation pattern. Furthermore, modification of the glycosylation pattern of immunoglobulins influences their effects on osteoclasts suggesting such strategies may allow to modify the effects of immune activation on the bone.

## IS2-5

### Immunological assessment for clinical trial of invariant NKT cell ligand

Sachiko Miyake<sup>1,2</sup>, Daisuke Noto<sup>2</sup>, Manabu Araki<sup>2</sup>, Wakiro Sato<sup>2</sup>, Tomoko Okamoto<sup>2</sup>, Miho Murata<sup>2</sup>, Takashi Yamamura<sup>2</sup>

<sup>1</sup>Juntendo University School of Medicine, Tokyo, Japan, <sup>2</sup>National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo Japan

Conflict of interest: Yes

Invariant NKT (iNKT) cells are a unique subset of lymphocytes that recognize a glycolipid antigen such as  $\alpha$ -galactosylceramide ( $\alpha$ GC) presented by monomorphic MHC class I-like molecule CD1d. iNKT cells are capable of producing diverse cytokines rapidly, depending on how they are stimulated, and lead to subsequent alteration of adaptive immune responses. We have previously demonstrated that an  $\alpha$ GC analog bearing a shorter sphingosine chain, OCH, that selectively induces IL-4 production from iNKT cells, showed a good efficacy for treatment of various autoimmune disease models including experimental autoimmune encephalomyelitis. Here we report on the immunological changes in the clinical trial of OCH for healthy subjects, which we have recently conducted in the NCNP. The aim of the study was to evaluate safety and pharmacokinetics of a single oral administration of OCH, and investigate alterations in immunological parameters and gene expression profiles. Fifteen healthy subjects were enrolled and allocated to 1 of 5 cohorts and given escalating doses of OCH. Mild leukopenia occurred in two subjects, but recovered without any treatments. All other adverse events were grade 1. Plasma concentration of OCH was much higher than anticipated based on preclinical study, indicating the bioavailability of OCH may be higher than rodents and primates. Flow cytometer analysis of lymphocyte subsets revealed that GM-CSF producing fractions in CD4<sup>+</sup> memory T cells and CD8<sup>+</sup> T cells were reduced after administration of OCH in all cohorts. IFN- $\gamma$  producing fraction in CD4<sup>+</sup> memory and CD8<sup>+</sup> T cells were also reduced in lower dose cohorts. DNA microarray analysis revealed that expressions of some genes associated with autoimmune responses were decreased, and some immunoregulatory genes were increased. The results were potentially interesting and allowed us to start an early phase 2 study for patients with multiple sclerosis (MS).

## IS3-1

### New Remission Criteria for Better Disease Control

Josef S. Smolen

Medical University of Vienna, Austria

When managing rheumatoid arthritis (RA), today's major treatment target according to EULAR and ACR is remission with low disease activity (LDA) by established criteria being an alternative. Remission ought to be defined as a state with no or at best minimal residual disease activity. Over the years, various remission criteria have been defined. ACR and EULAR have recently provided a new set of remission definitions (1) based on a Boolean approach with 4 or 3 variables (the latter without CRP) or on indices, namely the simplified and the clinical disease activity indices (SDAI, CDAI), the latter again not requiring CRP. These criteria comprise joint counts, given that the variable most closely associated with progression of joint damage is the swollen joint count. Using any of these ACR-EULAR remission criteria will lead to comprehensive disease control in terms of halting progression of joint damage, maximizing physical function and quality of life and minimizing risk of comorbidities, as has been consistently shown. An older remission definition, namely the one of the Disease Activity Score using 28 joint counts (DAS28) does not constitute a state of minimal disease activity, since the cutpoint of 2.6 allows for many residual swollen joints. Moreover, DAS28-“remission” frequencies mostly exceed 70% improvement by the ACR criteria, and sometimes ACR50 ranges, which provides high proportions of “remitters” but is counterintuitive, since it relates to patients having up to 29% (and sometimes 49%) residual disease activity. Indeed, patients in DAS28 remission who have swollen joints or do not fulfill SDAI remission criteria are characterized by progression of joint damage, higher disability scores and more frequent comorbidities. Moreover, while the DAS28 can be used by employing either ESR or CRP as the acute phase reactant, remission frequencies using the cutpoint of 2.6 often differ dramatically between these two variants, thus further casting doubt on the usefulness of these “remission” criteria. Finally, when using sonography to assess residual disease activity, patients in SDAI or Boolean remission have minimal residual power Doppler signals. In summary, using the ACR-EULAR definition of remission allows optimal disease control. Reference List (1) Felson DT et al.: American college of rheumatology/european league against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011; 70 (3):404-13.

## IS3-2

### Minimize structural damage to prevent functional disability

Désirée van der Heijde

Leiden University Medical Center, Leiden, The Netherlands

Conflict of interest: Yes

Structural damage in patients with rheumatoid arthritis is a hallmark of the disease. Damage is mostly seen on radiographs of hands and feet, and this is a good reflection of damage in large joints. Both bone and cartilage is affected and is visible as erosions and joint space narrowing respectively. Damage of the surrounding soft tissue such as ligaments and tendons can lead to joint luxation. Although the overall amount of structural damage over the last decades is diminishing, there is still a group of patients showing substantial damage. It is important to prevent this damage because there is a direct relationship between damage and physical function, and also with work disability. Both erosions and joint space narrowing contribute to disability, but joint space narrowing seems to have most impact. However, also the location of damage is important: damage in the wrist is more closely related to functioning than in other joints of the hands and feet. The various relationships between damage in small and large joints, with physical disability and work will be discussed. Data on patient level, but also based on data from individual joints will be presented.

## IS3-3

### Early Intervention – What are the prospects for cure?

Paul Emery

Leeds Institute of Rheumatic & Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom

Conflict of interest: None

The ultimate ambition of therapy for people with RA has always been cure. Traditional csDMARD therapy provided low rates of remission and consequently few opportunities for cure. Gold therapy produced remission, which persisted temporarily post-withdrawal of therapy, due to the accumulation of drug. The availability of biologics in particular those directed against TNF has led to remission-induction studies followed by withdrawal of drug with a small percentage of patients coming off therapy for prolonged periods. The original ambition of anti B-cell therapy (rituximab) was to produce cure by depleting the pathogenic B-cells. However, it is clear that although prolonged responses are seen in certain patients with RA they do all eventually relapse. The paradigm of early therapy and treating to target has led to a remission induction/subsequent drug-tapering approach. Despite impressive results only a minority remain in remission even if MTX is maintained. Therefore attention has turned to treating pre-RA for which it is necessary to accurately predict the development of RA; a great deal of work has been undertaken in this area. In some cases auto-antibodies precede the disease by many years. Progression to inflammatory arthritis in patients who are antibody positive is now being studied, and a number of biomarkers both clinical and sophisticated immunological ones with predictive value for progression have been identified. Therefore it is possible to stratify patients with the ambition of matching the risk of progression with the side-effects of the drug. The studies of intervention are limited but there is optimism that it will be possible to study disease modifying drugs with the aim of curing during this phase.

### IS3-4

#### Strategy after achieving complete disease control

Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational & Environmental Health, Japan

Conflict of interest: Yes

The combined use of synthetic DMARDs such as methotrexate (MTX) and biological DMARDs targeting TNF has revolutionized treatment of rheumatoid arthritis (RA) and clinical remission is realistic goals achieved by a large proportion of RA patients. After the induction into remission, the therapeutic strategies for the maintenance are required. However, there are concerns about long-term safety and economic burden associated with the maintenance therapy by biological DMARDs. Recent studies, including OPTIMA and HOPEFUL studies using adalimumab, indicate that the discontinuation of biological DMARD is possible without clinical flare and functional impairment for early RA patients after achieving remission. However, for patients with established RA, “deep remission” at the time of discontinuation is required to maintain the treatment holiday of biological DMARDs from RRR and HONOR studies. Because the complete discontinuation is rather difficult for the established RA, the de-escalation (dose reduction/interval prolongation) of biological DMARDs appears to attract attention to strategically treat RA. Thus, an intensive treatment would have the potential of reducing use of biological DMARDs as well as drug-induced adverse effects and long-term medical costs. However, the risks of worsening clinical, structural and functional outcomes should be considered with careful monitoring during de-escalation or discontinuation of synthetic and/or biological DMARDs.

## Educational Lecture

### EL1

#### Treatment strategies from accurate evaluation of disease activity of RA

Kazuyoshi Saito

The First Department of Internal Medicine, University of Occupational & Environmental Health, Fukuoka, Japan

Conflict of interest: Yes

With early therapeutic intervention using biologics and T2T strategy, clinical, structural, and functional remission has become a realistic goal. There are a number of metrics that we might use to assess RA. ACR response measures are commonly used in clinical trials and the Disease Activity Score which requires a formal joint exam and some fancy math. More practical measure is the Clinical Disease Activity Index, which is just a sum of the tender joint count, swollen joint count, patient global, and the physician global assessments and its variant SDAI which incorporates the C-reactive protein. Finally, there are patient-focused disease activity measures like the RAPID-3, where all of the information is coming from the patient and the physician doesn't have the requirement to do a formal joint exam and it doesn't require laboratory findings. In contrast, multi-biomarker disease activity (MBDA) quantify RA disease activity in the form of 12 biomarkers. We validated the MBDA scoring compared with DAS28 and confirmed the effectiveness on the evaluation of disease activity of RA in our cohort. Radiological evaluation has been employed by mTSS and recently assessment by ultrasound especially with power doppler method and MRI also provide important information of disease activity of RA. Quality of life is estimated mainly with HAQ (health assessment questionnaire) and productivity of labor is assessed by WPAI/RA (the Work Productivity and Activity Impairment questionnaire for rheumatoid arthritis) The appropriate evaluation of the disease activity is the most important point of the treatment strategy of T2T. But in real clinical practice, we experience the case that there is a lot of disagreement between patients' assessments and disease activity score. By this education lecture, I review the basic knowledge about the disease activity evaluation and give an outline about the important point in daily clinical practice.

### EL2

#### Surgical treatments for rheumatoid elbow regarding their indication and selection

Hiroyuki Kato

Department of Orthopaedic Surgery, Shinshu University School of Medicine, Matsumoto, Japan

Conflict of interest: None

The elbow joint is frequently involved by rheumatoid arthritis (RA). RA elbow causes elbow pain, disturbance for performing ADL such as washing face or hair, eating, and touching the buttock. The disabling status of the upper extremity with RA elbow is depend on function of the contralateral or ipsilateral upper extremity. Age, occupation, and dominant hand also affect disability of the elbow. Thus, surgical indication and procedures are different in each person even if the radiographic appearance is similar. Synovectomy is indicated in patients who are well controlled in their RA activity, however, whose elbow arthritis is not controlled. The elbow classified in Larsen grade II or III is indicated. When synovectomy is indicated in proper cases, reducing pain and improvement of function are achieved. Total Elbow Arthroplasty (TEA) is indicated to patients whose age over 40 years with RA elbow classified into Larsen grade IV or V. Pain and functional disability is necessary for indication. We have used Kudo elbow, unlinked type, to cases with good bone stock and without severe contracture or instability. Based on our results of 50 Kudo elbows, four Kudo elbows had to be removed due to infection or revision, and four elbows showed instability between both components, and three had obvious loosening around the ulnar component. Implant survival ratio in Kudo is 91% for 10 years. Kudo elbow achieved satisfactory results. However, there are several pit-falls in placement of ulnar component, soft tissue tension. For RA elbow out of indication of Kudo, we use Coonrad-Morrey (CM) elbow, linked type. Implant survival ratio in CM elbow is 93% for 5 years. CM elbow also



achieved satisfactory results. In cases with small elbow, we use DISCOVERY elbow instead of CM elbow. Current problems in TEA is revision surgery in case with poor bone stock. For these cases, we perform impaction bone graft with small pieces of allograft and hydroxyapatite.

### EL3

#### Paradigm-Shift in Patients with HBV and HCV Infection Complicating Rheumatoid Diseases

Satoshi Mochida

Department of Gastroenterology & Hepatology, Saitama Medical University

Conflict of interest: Yes

HBV prevails among populations in eastern. In such patients, serum HBV-DNA may become detectable following immunosuppressive therapies leading to development of liver damage, since cccDNA of HBV genome inevitably remains in hepatocytes even after transient HBV infection. The study group of the Ministry of Health, Welfare and Labour revealed that the cumulative rate of HBV reactivation defined was 3.2% at 6 months following the initiation of immunosuppressive therapies, and HBV reactivation seldom developed then later. Based on these observations, “the guideline for prevention of HBV reactivation” was revised in 2013; serum HBV-DNA measurements should be done every month within 6 months following the initiation and/or modification of the therapies, but the duration of the examination can be prolonged up to 3 months then later. However, mortal cases with acute liver failure due to HBV reactivation seen between 2010 and 2013 were still enrolled in the nationwide survey, and the patients especially due to immunosuppressive therapies were increasing in recent years. In contrast, antiviral therapies using interferon were unable to be done in patients with hepatitis C virus (HCV) infection complicating rheumatoid diseases in afraid of exacerbation of autoimmune reactions. In 2014, however, the dual oral antiviral therapy with asunaprevir and daclatasvir, NS3/4A protease inhibitor and NS5A inhibitor, respectively, was approved in Japan for the treatment of HCV infection. Recently, we established a novel simple assay system to predict therapeutic efficacy of the dual oral therapy through quantification of HCV strains showing amino acid mutations in the NS5A region. Based on these innovations in the field of antiviral therapies, HCV eradication can be achieved in safe in almost all patients even with autoimmune diseases such as rheumatoid arthritis.

### EL4

#### Managing and optimizing the biological treatment in rheumatoid arthritis

Tsutomu Takeuchi

Division of Rheumatology, Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan

Conflict of interest: Yes

The targeted therapy in rheumatoid arthritis (RA) is now widely accepted in clinical practice. Targeted synthetic and biological DMARDs provide powerful means to control disease activity, making clinical remission as a realistic treatment target in addition to conventional synthetic DMARDs such as methotrexate. However, it is not so easy really to achieve clinical remission within 6 months after starting a given drug in clinical practice and it is even true after adjusting and changing the drugs several times from the initial DMARDs. The treatment strategy for the patients having comorbidities and or experienced with the side effects of DMARDs should also be considered. In order to solve these difficulties, one direction may be to identify new targets with distinct efficacy and safety profiles over the existing known targets. In this symposium, I would like to focus on the new targets, on which the biological agents had been tested in early/late phase II trials with the positive results. For example, fully human monoclonal antibody against GM-CSF receptor, mavrilimumab, exhibited the excellent efficacy and acceptable tolerability in EARTH trial. By reviewing the result, the role of the targets, GM-CSF receptor and the ligands GM-CSF in pathogenesis of RA or inflammation are discussed. In addition, I shed light on another new target, RANKL. Fully monoclonal antibody against RANKL, denosumab, is already approved for osteoporosis, but the indication for RA has not yet

been obtained globally. Japanese clinical trial designated as DRIVE for the patients with RA has shown the positive results. By reviewing the core trial data for DRIVE and the updated new data, the significance and uniqueness of the target is discussed. Given these new information, I would like to add comments on the impacts of the new targets on the current treatment strategy and future perspective for RA therapy.

### EL5

#### Scleroderma

Shinichi Sato

Department of Dermatology, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo

Conflict of interest: Yes

Systemic sclerosis (SSc) is a connective tissue disorder characterized by fibrosis in the skin and internal organs. Although the pathogenesis remains unknown, collagen accumulation, vascular damage, and immune activation are major abnormalities. SSc is a heterogeneous disorder and, therefore, the subset classification is necessary for evaluating clinical manifestations, predicting prognosis, and selecting appropriate treatment. Specificities of autoantibodies are closely associated with clinical distinct subsets: anticentromere antibody is linked to limited cutaneous SSc (lcSSc), while anti-topoisomerase I or RNA polymerase antibody is associated with diffuse cutaneous SSc (dcSSc). Accumulating evidence has revealed the clinical natural course of each subset: skin sclerosis is very slowly developing for several decades without severe internal organ involvement in lcSSc whereas skin sclerosis and severe internal organ involvement, including lung fibrosis and scleroderma renal crisis, occur within first 5-6 years in dcSSc. Early diagnosis of patients with dcSSc is especially important since these patients may respond to treatment. Although treatment of SSc is generally difficult, there are some therapeutic choices that may be effective for patients with early dSSc. Oral low-dose steroid may be effective for skin sclerosis when it is used for early dSSc patients with edematous and rapidly progressing skin fibrosis. Although it is generally recognized that steroid is not effective for lung fibrosis, the controlled trial has shown that treatment with cyclophosphamide plus steroid is effective for patients with active lung fibrosis. Since it is difficult to remove fibrosis once fibrosis is established in SSc, it should be emphasized that early diagnosis and early treatment of dcSSc are critical for management of SSc.

### EL6

#### Autoinflammatory syndrome update

Ryuta Nishikomori, Takahiro Yasumi, Tomoki Kawai, Toshio Heike

Department of Pediatrics, Graduate School of Medicine, Kyoto University

Conflict of interest: None

The term “autoinflammatory syndrome” was first described by Dr. Kastner in 1999. The responsible genes of autoinflammatory syndrome are mainly involved in innate immunity, causing dysregulated inflammation. Its main clinical features consist of periodic fever, arthritis, gastrointestinal symptoms, and rashes, which would present a challenge for rheumatologists to differentiate autoinflammatory syndrome from rheumatic diseases and collagen diseases. Similarly to other hereditary diseases, the prevalence of the autoinflammatory syndrome is low. However, it is very important to diagnose autoinflammatory syndrome patients properly since specific therapy is available for some of them. Canakinumab for Cryopyrin-associated periodic syndrome (CAPS) is a good example. In addition, finding new genes for autoinflammatory syndrome brings new insight on disease mechanism of “more common diseases” by uncovering basic functions of the genes. NLRP3 inflammasome is identified as a disease-causing mechanism of CAPS, but later it is reported to be involved in more common diseases such as gout, Alzheimer’s disease, type 2 diabetes, and asbestosis. These findings demonstrate the importance of basic researches on Mendelian-inherited disorders. Recently new responsible genes for autoinflammatory syndrome have been discovered. It is due to completion of genome project and HapMap project as well as advancement of genetic analysis by next-generation sequencing, which enables us to dig out the candidate genes with a very few patients. In this talk, I

would like to focus on the autoinflammatory syndrome whose responsible genes have been recently identified (STING, ADA2, NLRC4) since these patients show some interesting clinical manifestations such as autoimmune phenomena observed in SLE, macrophage activation syndrome and Polyarteritis nodosa. In addition, I am going to highlight on the recent progress in medical service system surrounding the autoinflammatory syndrome in Japan.

## EL7

### Rehabilitation Approach for Patients with Rheumatoid Arthritis

Nobuhiko Haga

Department of Rehabilitation Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Conflict of interest: None

Rheumatoid arthritis (RA) affects multiple joints. Disability in affected joints is not simply the sum of disability in each joint. Mutual influence of each joints leads to decreased ADL and QOL. Therefore, in evaluating and treating patients, medical specialists must capture the overall perspective of the patient, in view of maintaining and improving ADL and QOL. Non-pharmacological and non-surgical treatments for RA include patient education, exercise therapy, physiotherapy, orthosis/assistive devices, balneotherapy, and acupuncture. All of these are strongly connected to rehabilitation medicine, which implies the importance of rehabilitation in managing patients with RA. Patient education by physiatrists, occupational therapists and nurses includes self-management to protect joints, such as how to open bottle caps, how to turn on the tap, and preferable height of chairs and pillows. Exercise therapy aims at maintenance/improvement of ROM, muscle strengthening, and increasing aerobic capacity. Dynamic exercise therapy, exercise therapy with a sufficient intensity, duration, and frequency, is effective in improving aerobic capacity and muscle strength, but disease activity should be considered in determining impact on joints. Physical and occupational therapy following musculoskeletal surgery is also important. As physiotherapy, thermotherapy plays a role on reducing pain and improving flexibility. The main object of electrotherapy is muscle strengthening. Most orthoses are prescribed to solve wrist/hand and foot problems. Orthoses can improve finger deformities and splints to fix joints can reduce pain. Foot orthoses can reduce pain and prevent deformity progression. Assistive devices include walking aids such as canes and special tools to be used in daily activities. The number of patients with RA living in community and receiving rehabilitation is decreasing. This lecture will give an outline of preferable rehabilitation approach for patients with RA.

## EL8

### A new era of reseache using induced pluripotent stem cells

Makoto Otsu

Center for Stem Cell Biology and Regenerative Medicine, Institute of Medical Science, University of Tokyo, Tokyo, Japan

Conflict of interest: None

Epoch-making development of strategies to generate induced pluripotent stem (iPS) cells has brought about a new wave in medical research. They would not only represent a candidate source of cells for regenerative medicine, but also provide us with an indispensable tool for basic research. This author has actually been utilizing iPS cell technologies in studying pathophysiology of, and in developing curative treatment for several genetic diseases including primary immunodeficiency. Another noticeable feature in iPS cell research is in the feasibility of reprogramming T cells to pluripotency (T-iPS cells). This means that researchers are practically able to obtain T cell clones by re-differentiating T-iPS cells, which would share the identical antigen-specificity with the original single T cells due to retention of the genetic recombination through the entire process. These “re-cloned” T cells would be utilized for a new generation immunotherapy against intractable infectious diseases and cancers. When these T-iPS cells are re-differentiated into T cells having inhibitory/regulatory functions, one could theoretically develop a novel therapy capable of inducing antigen-specific tolerance for patients with certain autoimmune diseases. In this lecture, these topics will be presented together with the basics regarding how to generate, maintain, and ma-

nipulate iPS cells.

## EL9

### Basic immunology for rheumatologists

Sachiko Miyake

Juntendo University School of Medicine

Conflict of interest: None

Immunology is a critical research field for the understanding the pathogenesis of rheumatic diseases. Recent advance in the treatment using biologics further feature the importance of being familiar with “Immunology”. In this lecture, starting from the quick review of basic immunology, the current topics in immunology will be addressed.

## EL10

### Current MR Imaging of the Articular Cartilage

Mamoru Niitsu

Department of Radiology, Saitama Medical University, Saitama, Japan

Conflict of interest: None

Strategies for imaging evaluation of the articular cartilage 1. Morphological evaluation of the cartilage High spatial resolution: 0.1-0.3mm in-plane resolution with 1-2mm section thickness or 3D isovoxel data set Using multi-channel coil, microscopy coil, 3T Precise section setting or 3 directional reformat from 3D data set High contrast resolution: bright fluid sequence and dark fluid sequence 2. Qualitative evaluation of the cartilage T2 mapping T1 mapping (dGEMRIC: delayed gadolinium enhanced magnetic resonance imaging for cartilage) T1ρ (spin-lattice relaxation time in the rotating frame) mapping CEST (chemical exchange saturation transfer)

## EL11

### Medical Ethics

Shinji Kosugi

Department of Medical Ethics and Medical Genetics, Kyoto University School of Public Health, Kyoto, Japan

Conflict of interest: None

Medical ethics deal this the following three fields. (1) So called “Research ethics” which is critical on medical research or introduction of new therapies. (2) So called “Clinical ethics” which is considered to be highly ethical by a number of health care professionals such as cancer notification. (3) There are a lot of ethical issues which have not been considered to be with ethical problems so far.

## EL12

### Basic lecture on cytokine and signal transduction

Hiroshi Takayanagi

Department of Immunology Graduate School of Medicine and Faculty of Medicine The University of Tokyo

Conflict of interest: None

Cytokines are mainly produced by immune cells and function as key regulators of function of other immune and non-immune cells. Antibodies or blockers of cytokine signaling have been applied to many rheumatic diseases including rheumatoid arthritis and contributed to the development of therapeutic advances in recent years. Here I will talk about the function, receptor and signal transduction of cytokines and provide molecular basis of therapeutics.

## EL13

### Genomics of autoimmune rheumatic diseases: an update

Naoyuki Tsuchiya

Molecular and Genetic Epidemiology, Faculty of Medicine, University of Tsukuba

Conflict of interest: None

In this educational seminar, I will focus on autoimmune rheumatic diseases other than rheumatoid arthritis, and briefly summarize recent advances of genetics and genomics studies. Systemic lupus erythematosus has a long history of candidate gene studies, followed by genome-wide association studies. Altogether, these studies led to the identification of >70 genomic regions of convincing association. Currently, some of the regions are being fine mapped to identify causal functional variants. As of December 2014, GWAS from Japan has not been published on systemic sclerosis, ANCA-associated vasculitis and polymyositis/dermatomyositis, although one or several GWAS have been reported from European populations. With respect to diseases rather frequent in Japan such as Behçet disease, Kawasaki disease and Takayasu arteritis, GWAS from Japan have been reported. These studies revealed insightful findings, including that the genetic background appears to be substantially shared among multiple immune system disorders. These studies also emphasized the importance of *HLA* region as the strongest genetic factor for many of the immune system disorders, and re-inspired detailed studies of this region. Recently, exome analyses on rare diseases with features of autoimmune or autoinflammatory disorders revealed gain-of-function mutations of type I interferon induction pathway genes such as *STING* for STING-associated vasculopathy with onset in infancy (SAVI) and *IFIH1* for Aicardi-Goutières syndrome. Such studies will shed light on the molecular mechanism of autoimmunity of autoinflammation, and may potentially lead to the identification of molecular targets.

#### EL14

##### Update on molecular target therapy for RA

Kunihiro Yamaoka

Division of Rheumatology, Keio University School of Medicine

Conflict of interest: Yes

Biologics (BIO) are frequently used as molecular targeted therapy for rheumatoid arthritis (RA). Based on the experience and evidence with BIO in daily practice for more than a decade, new strategies such as dose reduction, discontinuation and concomitant disease modifying anti-rheumatic drug (DMARD) are on the table. New BIO such as fully humanized anti-IL-6 receptor antibody (Ab), anti-IL-6 Ab, anti-GM-CSF Ab and bispecific Ab are on their way. On the other hand, small molecule compounds targeting cytoplasmic kinases are actively explored. Especially, Tofacitinib targeting the Janus kinase (JAK) has demonstrated treatment effect resembling BIO and has been approved in over 30 countries following approval in the US and Japan. Since JAK deficiency is known to result in immunodeficiency, likewise other anti-rheumatic drugs, meticulous care for excessive suppression is required. Since Tofacitinib is a new DMARD with a novel mode of action, its side effects have gathered attention. Infection and malignancies are the two major concerns at the time being. Herpes zoster is increase especially in the elderly and number of gastric cancer is higher with slightly increased cancer rate in Japan compared to the western countries. However, since patient numbers are still low, careful observation is necessary. There are four JAKs, JAK1, JAK2, JAK3 and Tyk2 that form different dimers in the cytoplasm depending on various cytokines. Therefore, different specificity of the compound might enable the delivery of better efficacy with fewer side effects. Clinical trial with Baricitinib (JAK1/JAK2-inhibitor), ASP015K (JAK1/JAK3-inhibitor) and GLGP0634 (JAK1-inhibitor) is under way, however, they have shown similar efficacy and side effects with Tofacitinib. Thus, we do not yet have an answer for differentiation of JAK inhibitors. Further progression with these new DMARDs is expected after the decade of great breakthrough in evolution of RA treatment.

#### EL15

##### Osteoporosis treatment: an update

Sakae Tanaka

Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo

Conflict of interest: Yes

Japan is one of the most aging countries in the world, and the proportion of people aged over 65 years old in the total population is highest in the world. By 2030, one in every three people will be over 65 years old and one in five people over 75. The aging of the society results in the increase in the number of osteoporosis patients, and more than 12 million osteoporosis patients exist in Japan. For aged people, to maintain mobility is critical for keeping independence, and osteoporotic fractures such as vertebral fractures and hip fractures are major causes of disability, morbidity and mortality in older people. The treatment of osteoporosis by anti-resorptive agents such as second and third generation bisphosphonates and denosumab successfully reduces the osteoporotic fractures. However, the fracture prevention using these agents is not sufficient and several adverse events have been recognized. Teriparatide is an anabolic reagent which efficiently increases bone mass by stimulating novel bone formation, and prevents osteoporotic fractures. Recent studies have revealed an additive effect of denosumab and teriparatide on BMD. In addition, new therapeutics with distinct mechanisms of action have been reported and attracted a great deal of attention.

#### EL16

##### An update on Behçet disease

Hajime Kono

Department of Internal Medicine, Teikyo University School of Medicine

Conflict of interest: Yes

Behçet disease is a chronic inflammatory systemic disorder, characterized by a relapsing and remitting course of manifestations of oral and genital ulcerations, skin lesions, uveitis, and vascular, central nervous system and gastrointestinal involvement. The main histopathological finding is a widespread vasculitis of the arteries and veins of any size. Both of the environmental and genetic factors are implicated in the pathogenesis of Behçet disease. Among the environmental factors, infectious agents are proposed to play roles. HLA-B51 is shown to be the strongest associated genetic factor, and several susceptibility genes are found to be associated with Behçet disease including IL-10, IL23R-IL-12RB2, CCR1/CCR3, MEFV, TLR2, TLR4 and vitamin D receptor. In addition, epigenome-wide screening indicated that DNA methylation alterations in cytoskeletal dynamics contribute the pathogenesis of the disease. As the clinical expression of Behçet disease is heterogeneous, pharmacological therapy is variable and depends largely on the severity of the disease and organ involvement. CNS involvements are classified as acute and chronic manifestations. Acute attack of CNS can be treated with glucocorticosteroids. Chronic progressive neuro Behçet does not respond to glucocorticosteroids, but can be treated with low dose pulse methotrexate. Anti TNF $\alpha$  therapy was shown to be effective in refractory uveitis, gastrointestinal, neurological and vascular involvements that certainly improves the outcome of the Behçet disease. Recent retrospective observations show that withdrawal of infliximab after the remission of uveitis promising results. Although the management of patients with Behçet disease has been improving over last decade, the treatment remains challenging partly because of the lack of solid evidences. Better understating of molecular mechanisms of the disease is also awaited.

#### EL17

##### Public program for citizen and medical partnership in rheumatoid arthritis

Hideki Nakamura

Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences

Conflict of interest: Yes

Because management of rheumatoid arthritis (RA) has been rapidly changed after introduction of high dose methotrexate or biologics, education regarding RA practice toward RA patients and their support is necessary. Meanwhile, change of awareness by medical staff and flexible response toward rapid alteration are required. Nagasaki has isolated islands and lacks sufficient rheumatologists; therefore we started a public program for citizens. The program goes around every 6 months considering the geographical condition. The program consists of 3 parts including lectures by rheumatologists, pharmacologists, demonstration of exercise

for RA, questions and answers. Pre-questionnaire showed participants' situation and provided reference for improvement of the program. A coalition between primary care doctors and lodgment hospitals that is reported by a task force of RA and Allergy in the Ministry of Health, Labour and Welfare is desired. Increase in complexity of RA care and devoting effort to secure doctors made us concern to secure environment for base research, leading to its formula and we launched this system in 2010. After we sent prospectus to facilities, confirmation of wishes and creation of available medicines were conducted. Treatment was introduced in University and we started the coalition regarding patients with low disease activity or remission. Double medical care is a basic strategy, biannual meetings with doctors of coalition facilities were set up, mini-lectures were performed and discussion period was held. Over 100 patients treated with MTX or biologics were in this partnership with 37 facilities over 3 years. A part of facilities utilize 'Ajisai net' for information sharing. In 3 years, no exacerbation of RA was observed. Though emergency in holidays is accepted in University Hospital because many facilities are operated as clinics, only one case admitted University by adverse events, suggesting effective medical coalition system is going on.

### EL18

#### Total hip arthroplasty for patients with rheumatoid arthritis

Isao Matsushita, Hiraku Motomura, Tomoatsu Kimura  
Department of Orthopaedic Surgery, Faculty of Medicine, University of Toyama

Conflict of interest: Yes

Hip joint is very important for walking ability, and damage to this joint deteriorates ADL and QOL remarkably. It is necessary to perform detailed radiographic assessment of hip joint to decide the appropriate timing of surgical intervention for patients with RA. We have already reported that hip joints with pre-existing Larsen grade III/IV damage show apparent radiographic progression in spite of enhanced medical treatment and tight control. Therefore, appropriate judgement of surgical timing for hip joint should be performed before progression of walking disability. Total hip arthroplasty (THA) has been considered as the gold standard treatment for damaged hip joint of RA. It has been demonstrated that clinical and radiographic results of THA in patients with RA are mostly satisfactory. Several studies indicated that THA in patients with RA showed good survival rates with the endpoint of aseptic loosening or revision during mid- or long-term follow-up. It has been argued whether cemented THA was superior to cementless THA for patients with RA. However, there was no evidence that cementless THA is inferior to cemented THA. Guidelines for the management of rheumatoid arthritis, JCR 2014, recommend both cemented and cementless THAs for damaged hips in patients with RA. In this session, I would like to talk about appropriate timing of surgical intervention, effectiveness and pitfall of THA, and our efforts to restore damaged hips of patients with RA.

### EL19

#### IgG4-related disease

Hiroki Takahashi  
Department of Gastroenterology, Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine, Sapporo, Japan

Conflict of interest: None

IgG4-related disease (IgG4-RD) is a systemic chronic disease characterized by tumefactive lesions, elevated levels of serum IgG4, and prominent infiltration of IgG4-positive plasma cells with fibrosis. Both lacrimal and salivary glands, and pancreas are the most affected organs during clinical course of IgG4-RD. Lacrimal and salivary gland disease formerly termed "Mikulicz's disease" and autoimmune pancreatitis had been treated as single organ disease. Existence of common characteristics associated with IgG4 and frequent overlapping of both diseases has contributed to establishment of IgG4-RD as a systemic entity. Patients with IgG4-RD are often asymptomatic at early stage and constitutional symptoms are rarely observed. Typical facial appearance, oral thirsty and submandibular swelling are helpful initial symptoms leading to diagnosis. Suspecting IgG4-RD based on the swelling of various organs, the measurement of serum levels of IgG4 and histopathological examinations in-

cluding immunostaining with anti-IgG4 antibody are performed, and diagnosis should be identified according to a comprehensive diagnostic criteria. In addition, careful examination is necessary to exclude other disorders such as malignancy. Although organ damage in IgG4-RD was thought to be reversible with good responsiveness to glucocorticoids (GC), delay in treatment intervention causing irreversible dysfunction has been reported. Accordingly, significance of early diagnosis and therapy has been recognized. Although the first line treatment for IgG4-RD is empirically administration of GC, careful observation without treatment could be possible considering age and complications. However, severe organ damages such as obstructive jaundice and hydronephrosis are an absolute indication for prompt intervention of GC. Multiple organ involvement and subjective symptoms also require the treatment. I would like to introduce unique clinical characteristics of IgG4-RD and mention future issues.

### EL20

#### How to use methotrexate: ABC in medical practice for the patients with rheumatoid arthritis

Shinichi Kawai  
Division of Rheumatology (Omori), Department of Internal Medicine, Toho University School of Medicine, Tokyo, Japan

Conflict of interest: Yes

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by proliferation of the synovium and the progressive destruction of cartilage and bone resulting in impaired quality of life. The treatment of RA is still unsatisfactory, but a number of powerful disease-modifying anti-rheumatic drugs including biological agents have become available. Even in the current era of biological targeted therapies, methotrexate (MTX) remains the initial preferred anti-rheumatic drug which is introduced in several recent guidelines and/or recommendations such as "Guidelines for the Management of Rheumatoid arthritis 2014" by Japan College of Rheumatology. MTX is considered to be the gold standard for treatment of RA as monotherapy and also as combination therapies with other anti-rheumatic drugs. The efficacy, safety profile, and low cost, as well as a plenty of clinical evidence and experience, makes MTX the anchor drug in the drug therapy for RA. In this lecture, mechanisms of action of MTX and our recent research in the field of clinical pharmacology of MTX according to the intracellular metabolism and gene polymorphisms of the related enzyme in RA patients will be introduced. How to use MTX will then be summarized based upon the therapeutic strategies in medical practice for effective management of RA.

### EL21

#### Biologic agents in the treatment of children with rheumatic diseases. Six years experiences in Japan

Syujii Takei  
School of Health Sciences, Faculty of Medicine, Kagoshima University, Kagoshima, Japan

Conflict of interest: None

Six years have passed since the first biologic agent was approved in the treatment of juvenile idiopathic arthritis (JIA) in Japan. At present in 2015, 4 biologic agents of Tocilizumab (TCZ), Etanercept (ETN), and adalimumab (ADA) were approved for JIA, and Canakinumab was for cryopyrin-associated periodic syndrome (CAPS). In addition, 2 clinical studies of Abatacept (ABT) for JIA and TCZ for Takayasu's arteritis are undergoing. Advantages of biologic agents were remarkable in both RA and JIA patients in improving joint symptoms and in preventing regression of joint damage. In case of JIA patients, biologic agents promoted height growth and increased the bone mineral content. In addition, they also improved the QOL especially in school activities; which may promise the high levels of QOL in daily lives and to increase the rate of employment in their future. Biologic agents also brought drug-free remission in some JIA patients who had been refractory to the conventional therapy. For CAPS patients, Canakinumab may prevent to develop to severe amyloidosis through the long-term continuous therapy. Furthermore, the official support program for children with rheumatic diseases, recently-renewed by Japanese government, enables the use of the expensive

medication of biologic agents. As the experiences of biologic therapy for children with rheumatic diseases accumulated, clinical importance of early intervention of specific treatment for JIA children increased. However, there are very few pediatric rheumatologists in Japan, as the result, more than 90% of JIA patients with polyarthritis referred to adult orthopedic surgeon. In addition, a new medical issue of 'transition from pediatrician to adult physician' is raised for the patients who had carried their rheumatic diseases over their adulthood. Thus, induction of biologic agents in the treatment of children with rheumatic diseases is requiring the close mutual contact between pediatric and adult rheumatologists.

## EL22

### Best practice to improve treatment outcomes in patients with pulmonary hypertension: the practical essence for rheumatologists

Masataka Kuwana

Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine

Conflict of interest: Yes

Pulmonary hypertension (PH) is a heterogeneous condition with increased pressure in the pulmonary arteries, which leads to right heart failure and low cardiac output. PH is currently classified into many categories, including pulmonary arterial hypertension (PAH), pulmonary veno-occlusive disease, PH owing to left heart disease, PH owing to lung disease and/or hypoxia, chronic thromboembolic PH, and PH with multifactorial mechanisms. All PH forms can occur in patients with connective tissue disease (CTD), but PAH is the most common. Prognosis of PAH is very poor if remain untreated, with a survival of 50% at one year and <20% at 3 years after diagnosis. Recent introduction of molecular-targeting PAH drugs, such as prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, has prolonged time to clinical worsening and survival, but PH still remains an intractable condition. To further improve outcomes, early detection and diagnosis, and personalized treatment approaches are essential on the basis of recognition of complexity of PH associated with CTD. Since patients with CTD are at high risk for developing all forms of PH, rheumatologists must play a central role in management of PH associated with CTD. One of the major roles of rheumatologists in the PH management is to identify patients with early PH by active screening program, since patients with systemic sclerosis or mixed connective tissue disease are at an extremely high risk of developing PH. In addition, rheumatologists have to play an important role in optimizing treatment regimens for PH, by taking account of PH classification, disease subset and activity of underlying CTD, concomitant interstitial lung disease and myocardial dysfunction, and safety profiles of PAH drugs, in the joint forces with cardiologists and/or pulmonologists.

## EL23

### Lung involvement in connective tissue diseases

Hiroshi Mukae

Department of Respiratory Medicine, University of Occupational and Environmental Health

Conflict of interest: Yes

Lungs are frequently involved in connective tissue diseases (CTDs), especially rheumatoid arthritis (RA), with a noticeable effect on morbidity and mortality. Interstitial lung disease (ILD) is one of the most common pulmonary manifestations. ILD associated with CTDs (CTD-ILD) includes histopathologically non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), diffuse alveolar damage (DAD), organizing pneumonia (OP) and so on. It is well known that detailed analysis of radiological findings using HRCT is useful to estimate histopathological sub-classification in CTD-ILD. The most frequent radiological/histological patterns of CTD-ILD include: NSIP; UIP; OP seen in polymyositis/dermatomyositis (PM/DM) and RA; and DAD seen in RA and PM/DM, especially amyopathic DM. In addition, evidence suggests that a UIP pattern in RA may be associated with shorter survival than that in other CTDs. In addition, several drugs may cause lung reactions in the treatment of CTDs. For example, MTX-induced ILD occurs with a frequency ranging from 0.3 to 11.6% during the first year of treatment. On

the other hand, patients with RA have been reported to have an increased risk of developing infections compared with non-RA subjects (bacterial pneumonia, *Pneumocystis* pneumonia, mycobacterial and fungal infections). This may be due to immunomodulatory effects of RA, or to agents with immunosuppressive effects used in its treatment. Thus, especially, acute-onset diffuse lung involvement in patients with RA has been a serious concern, especially for those under treatment with biological agents. Therefore, all new RA patients and the patients who have a new complaint of respiratory symptoms should be assessed by a chest X-ray and CT. In this lecture, I will focus on lung involvement in CTDs, especially RA, with particular attention to ILDs and infections, and make a presentation of their prevalence and clinical manifestations, as well as therapeutic approaches to them.

## EL24

### Cutaneous manifestations of rheumatic diseases

Tetsuya Tsuchida

Department of Dermatology, Saitama Medical University, Moroyama, Japan

Conflict of interest: None

For the diagnoses of rheumatic diseases, it is important to see the eruptions on the faces and hands of patients carefully. The appropriate evaluation of these skin manifestations may lead to even the definite diagnosis of rheumatic diseases. Another important point is to consider the common pathogenesis among the various skin manifestations. By understanding the various eruptions as spectrum, it becomes easier to evaluate those skin manifestations. The cutaneous manifestations of rheumatic diseases are classified into specific eruptions and unspecific ones. The specific eruptions are important for the definite diagnosis of the disease. Unspecific eruptions are often related with the abnormal peripheral circulation and are helpful in the early diagnosis. In this lecture the significance of the cutaneous manifestations of rheumatic diseases in diagnosis and disease activity will be mentioned especially on lupus erythematosus (LE). The terms for eruptions and those for diagnoses in LE should be used separately. The specific eruptions of LE are classified into chronic cutaneous LE (CCLE), subacute cutaneous LE (SCLE) and acute cutaneous LE (ACLE) as one axis. CCLE includes discoid LE (DLE) and so on. On the other hand the terms for diagnoses named from the standpoint of systemic manifestations include systemic LE (SLE) and so on as another axis. Then the two dimensional classification system for LE is proposed. In this classification system, the condition of each LE patient is evaluated both in systemic and cutaneous standpoints. Annular SCLE in Caucasian and Sjögren's annualr erythema in Oriental have the common pathogenesis associated with anti-Ro (SS-A) antibodies. The cutaneous manifestations of dermatomyositis are featured by deposition of mucin and mechanical induction. Nail-fold bleedings are unspecific, but are important for early signs in systemic sclerosis and dermatomyositis. The features of eruptions in adult-onset Still's disease are also discussed.

## EL25

### Osteoarthritis ABC: The epidemiological study ROAD

Noriko Yoshimura

22nd Century Medical and Research Center, The University of Tokyo

Conflict of interest: None

Osteoarthritis (OA) is a major public health problem in the elderly. It affects ability to perform activities of daily living (ADL), as well as quality of life (QOL), leading to increased morbidity and mortality. In Japan, the prevalence of OA is increasing as the population ages, and the most recent National Livelihood Survey conducted by the Ministry of Health, Labour and Welfare ranks it fifth among diseases that cause disabilities requiring support. Therefore, there is an urgent need for a comprehensive and evidence-based strategy for prevention of musculoskeletal diseases, including OA. However, few prospective longitudinal studies have been undertaken in this field, and little information is available regarding the prevalence and incidence of OA, lumbar spondylosis, and their associated pain and disability in the Japanese population. The Research on Osteoarthritis-osteoporosis Against Disability (ROAD) study was established from 2005 to 2007 (baseline study). It was a prospective cohort study

aiming to elucidate the environmental and genetic background of bone and joint diseases, such as OA. It was designed to examine the extent to which risk of these diseases was related to clinical features, laboratory and radiographic parameters, bone mass and bone geometry, lifestyle, nutritional factors, anthropometric and neuromuscular measures, and fall propensity, as well as to determine how these diseases affect ADL performance and QOL in Japanese men and women. Following the baseline study, we performed a second survey in the same communities from 2008 to 2010, followed by a third survey from 2012 to 2013. The present study aimed to estimate the essential indices of epidemiology of OA, such as prevalence and incidence of knee OA and lumbar spondylosis, and their related risk factors. In addition, the associations of musculoskeletal diseases with metabolic syndrome are elucidated using the latest ROAD follow-up data.

## EL26

### How to apply animal models with rheumatic diseases to the clinical medicine

Isao Matsumoto

Department of Internal Medicine, Faculty of Medicine, University of Tsukuba

Conflict of interest: Yes

Animal models of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are widely used for testing potential new therapies, and get a prominent outcome in our field. It is true that biologics targeting inflammatory cytokines, T cell, and B cells change the prognosis of patients with RA, and after that, there is a trend such as “clinic to bench” to reconsider the pathogenesis and pathophysiology of rheumatic diseases, leading to the application for the common pathway to the other rheumatic diseases. The etiology of rheumatic diseases is diverse, mixed with genetic factors, environmental factors, cells and proteins, it is impossible to find out the perfect animal models. Probably most of the animal models reflect a part of the feature of the pathogenesis in vivo. Thus, we need to understand what parts of animal models are really mimicked to human etiology to complete our task. In this seminar, I will summarize recent update of the pathogenesis of rheumatic diseases especially RA, and discuss about feature and application point of representative animal models that contribute to find out the new therapeutics and pathogenesis to the diseases.

## Meet the Expert

### MTE1

#### The practical assessment of synovitis by ultrasound

Shigeru Ohno

Yokohama City University Medical Center, Center for Rheumatic Diseases

Conflict of interest: None

Musculoskeletal ultrasound (MSUS) is a sensitive method for the detection of both early inflammatory soft tissue lesions (eg, synovitis, tenosynovitis, and bursitis) and early bone lesions (eg, erosions) in arthritic joint diseases. Accurate assessment of disease activity and joint damage is important for monitoring treatment efficiency and for prediction of the outcome of the disease. On the other hand, it is widely known that MSUS is highly operator dependent as well as time-consuming. In clinical practice, semiquantitative four-grade system is frequently used, but with lack of definition of each grade among various joint lesions, there are intra- and inter-observer variabilities in the grading of synovitis. Is it reasonable to do MSUS frequently in most RA patients in busy daily practice? How important it is to differentiate moderate synovitis and mild synovitis? The important point to diagnose RA early and evaluate remission is to detect the presence of subclinical synovitis and not to grade the level of synovitis. Rheumatologists can judge the change of disease activity by clinical examination. The most important thing that MSUS tell us is the presence of subclinical pathology. Most of moderate to severe MSUS synovitis could be judged by clinical examination. It is important to understand the merits and demerits of MSUS and to use MSUS as a complementary tool in clinical practice and research.

### MTE2

#### Reconstruction of Elbow and Hand with total joint arthroplasty for patients who have rheumatoid arthritis

Katsunori Inagaki

Department of Orthopedic Surgery, Showa University School of Medicine

Conflict of interest: None

Rheumatoid arthritis has been easily under control by drug therapy. However, when we look at the joint function and deformity for mid-term and long-term, quality of life in patients who have rheumatoid arthritis is still not so high. This program provides the natural course of deformity, surgical indication and treatment for deformity in elbow joint and hand with rheumatoid arthritis. We also suggests the efficacy of total elbow arthroplasty and total MP and PIP arthroplasty for these deformity and dysfunction.

### MTE3

#### How to handle methotrexate in rheumatoid arthritis

Naoto Tamura

Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine, Tokyo, Japan

Conflict of interest: Yes

The intermittent use of low dose methotrexate (MTX) with folic acid has been contributing to the dramatic progress of treatment for rheumatoid arthritis. In Japan, MTX was approved up to 16 mg /week as a first-line DMARD in Feb 2011, and then, making the best use of MTX has been becoming more and more important. After the intracellular uptake, MTX is polyglutaminated at the site of original glutamine indicated to have medicinal actions. It takes several weeks from commencement of MTX to achieve the steady concentration of MTX-PGs, suggesting that the dose of MTX must be escalated quickly to obtain the appropriate effects. Screening of hepatic viruses and tuberculosis is necessary before starting MTX. Pregnancy should be avoided at least for 3 months after cessation of MTX. The side effects of MTX is more frequent in patients with renal dysfunction. It is important to give patients previous information that MTX should be skipped in case of having high fever or acute gastroenteritis that possibly induces dehydration. In patients having poor

prognostic factors, MTX is started with 8 mg/week and increased every 2-4 weeks up to 16 mg if it is tolerable. Folic acid should be added when MTX is used 8 mg/week and over, and patient has risk factors for the side effects. Dose-dependent adverse events, such as digestive symptoms, elevation of liver enzymes and cytopenia, may be observed. Liver enzymes is possibly raised by reactivation of HBV in patients with the past infection. MTX pneumonia may be associated with existing lung diseases, aging, diabetes, and low albuminemia. Prevention of pneumocystis pneumonia is necessary in the high risk patients. Daily education is important to find such infections earlier. MTX-related lymphoproliferative disease can be recognized once in a while. In this seminar, I would like to show case presentations and discuss with the participants to deepen the comprehension of MTX treatment.

#### **MTE4**

##### **Examination of joint findings**

Ayako Nakajima

Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: None

The roles of image examinations including articular echography or magnetic resonance are getting larger in the field of rheumatology. However, these imaging examination cannot be performed at anytime and in any place. The basic way of treating patients is to listen to patient's symptoms carefully and then examine patient thoroughly by using physician's eyes, ears, and hands. It is important for rheumatologists to make diagnosis and evaluate disease activity based on these clinical findings and succeedingly complimented by the results of blood tests and images. In clinical examination, it is important to evaluate whether pain, stiffness or swelling which patient complained come from joint or other tissues such as muscle, tendon, enthesitis, or dactylitis and coexisting skin lesions. Physicians must pay attention to patients' reaction by seeing their face whether the examination may cause pain. Many other joints other than 28 joints are need to be examined for redness, warmth, swelling, tenderness, and range of motion. Sometimes patients feel swelling of joint before physician can capture the swelling. In such condition, re-examination after a certain period may help to detect findings. It may not enough to evaluate joint swelling just as present or absent in the course of treatment, as joint swelling changes in response to treatment. Thompson P et al proposed to evaluate swollen joint in 4 grades (Arthritis Rheum 1987;30: 618). It is still difficult to evaluate joint findings. In these days, physician can access results of blood examination before seeing patients, however, I still think that it is important to evaluate patient's disease activity through patient complaint and joint findings in advance before seeing the results of laboratory data.

#### **MTE5**

##### **The pathophysiology and treatment of osteoarthritis: up-to-date**

Hiroshi Kawaguchi

Japan Community Health Care Organization (JCHO), Tokyo Shinjuku Medical Center

Conflict of interest: None

The disease-modifying treatment has not been established for the osteoarthritis (OA) treatment. Using mouse experimental OA models, others and we confirmed that the endochondral ossification process, which is not seen in the joint cartilage but is an essential step for skeletal growth, was induced during the OA development. To identify signals to induce endochondral ossification, we performed a screening of transcription factors, and identified hypoxia-inducible factor 2 $\alpha$ (HIF2A) as the most potent inducer. Recent mouse genetic approaches by others and us found that other endochondral ossification signals like Runx2, carminerin, osteoprotegerin,  $\beta$ -catenin, syndecan-4, hedgehog, etc. are involved in the OA development. We have recently found that Notch signaling in chondrocytes controls cartilage degradation during OA development, representing an extracellular therapeutic target of OA. In addition, teriparatide (PTH) injection is reported to inhibit chondrocyte hypertrophy and OA progression. At the periphery of the joint, vascularity is accessible from the synovium or tendon, which completes endochondral ossification and forms osteophytes. However, in the center, the vascularity is not accessi-

ble from the edge, so that it may end up with cartilage degradation without being replaced by bone. Molecules related to the endochondral ossification signals might become therapeutic targets altering the course of this disabling disease. For the time being, there are several international treatment guidelines for OA. Among them, the OARSI guideline has kept providing us with new evidence. In this lecture, I introduce the newest 2014 OARSI treatment guideline (part IV). Besides these international guidelines made by Western countries, there is a Japanese OA treatment guideline. These guidelines showed a substantial difference, especially hyaluronic acid injection and supplements like glucosamine and chondroitin sulfate.

#### **MTE6**

##### **Strategy of the joint reconstruction surgery in biologic era**

Naoki Ishiguro

Department of Orthopaedics and Rheumatology, Nagoya University, School of Medicine, Nagoya, Japan

Conflict of interest: None

Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by articular joint involvement, which leads to function impairment of human body. The recovery of function was gained with joint surgery such as joint replacement. The recent developed therapeutic methods may change the situation in recent onset RA patients. However, previous studies demonstrated the various pattern of disabilities led to the limitation of living life and QOL impairment in patients with established RA patients. Even now, in clinical practice, most of RA patients have long-standing disease and structural damage in their joints. Reconstructive joint surgery should be needed for further improvements of physical function for long-standing RA patients. Because the reconstructive surgery may have only the limited effects on the disabled condition with established RA. It is very important to understand how much range of motion (ROM) should be needed to gain better physical function in each case.

#### **MTE7**

##### **Management of lymphoproliferative disorders**

Michihide Tokuhira

Saitama Medical Center, Saitama Medical University

Conflict of interest: None

The disease category of lymphoproliferative disorders (LPDs) is composed of the lymphoid abnormalities including lymphomas, and a number of LPDs has been recently reported in the patients with autoimmune diseases under methotrexate (MTX) administration. The various LPD phenotypes are observed so that it is generally named as MTX-LPDs. MTX-LPDs are commonly developed in the patients with rheumatoid arthritis (RA) patients. The 4th edition of the WHO classification proposes the entity of immunodeficiency-associated LPDs along with 4 subcategories, and MTX-LPDs are categorized in "other iatrogenic immunodeficiency-associated LPDs". Although the retrospective analysis reveals the clinical manifestations, the basic etiology of this disease has not been unsolved yet. The demonstrated clinical findings are: 1) the development of MTX-LPDs is not related to the factors such as the duration of RA, MTX dose and the MTX duration, 2) LPDs often indicate the various atypical phenotypes, 3) the discontinuation of MTX conducts the regression of LPDs (40% of the patients), 4) LPDs occasionally flare within a year, 5) the chemotherapy is commonly required in the patients with remaining or flared LPDs, resulting in a high ratio of complete response, 6) the stable disease is sometimes observed, 7) Epstein-Barr Virus (EBV) is thought to be one of the etiologies, and a strong relationship is demonstrated between EBV positivity and Hodgkin lymphoma, 8) anti-RA drugs might be required after MTX discontinuation within a year, 9) anti-RA drugs might be independent of the relapsed LPD phenomenon. From our analysis, the prognostic factors were the age, serum LDH, sIL-2, and CRP at the development of LPDs. Some patients who resulted in delayed diagnose with uncompleted therapy might be effected to the prognostic factors. The MTX cessation is very important to improve the outcome if the LPD developed manifestations such as fever, CRP, and LDH elevation are observed.

## MTE8

### Rehabilitation for the patients with rheumatoid arthritis

Ryuichi Saura<sup>1,2</sup>, Kana Nagao<sup>2</sup>, Miyuki Murakawa<sup>3</sup>, Tetsuya Hinoshita<sup>2</sup>, Hiroshi Ohno<sup>3</sup>, Koji Horaiya<sup>5</sup>, Yuka Iwai<sup>2</sup>, Yuko Tamura<sup>2</sup>, Taro Tohchika<sup>2</sup>, Yasuko Ohnishi<sup>2</sup>, Haruki Nakano<sup>1,2</sup>, Masao Tomioka<sup>1,2</sup>, Michiaki Takagi<sup>3,4</sup>, Daisuke Itoh<sup>2</sup>, Yuji Oda<sup>2</sup>

<sup>1</sup>Department of Physical and Rehabilitation Medicine, Division of Comprehensive Medicine, Osaka Medical College, Osaka, Japan, <sup>2</sup>Department of Rehabilitation, Osaka Medical College Hospital, Osaka, Japan, <sup>3</sup>Rehabilitation Unit, Yamagata University Hospital, Yamagata, Japan, <sup>4</sup>Department of Orthopaedic Surgery, Yamagata University Faculty of Medicine, Yamagata, Japan, <sup>5</sup>Department of Rehabilitation, Hokusetsu General Hospital, Osaka, Japan

Conflict of interest: Yes

Aim of the rehabilitation is to let the peoples with any disabilities live as usual humankind by diminishing or compensating the difficulties in daily life. Protraction of RA induces the disorders of joint function. As a result, activities of daily living (ADL) are deteriorated, which yields the limitation of social participations. Functional disorders have once developed, a plural number of it make disabilities worse. Therefore, in order to prevent the progression of these problems, Along their disease activities and progressions, RA rehabilitation includes the various kinds of approaches such as patient education, exercise therapy, application of splints and utilization of long-term care insurance. In late years, it is reported that the high effectiveness of biological agents such as TNF blockers for RA. When the structural remission following the clinical one has been successfully introduced by the biological agents, the problems confronting the execution of rehabilitation might be reduced. However, even if RA patients have achieved their clinical remission by biological agents, joint destruction might progress rapidly by overuse of it when it had been damaged beyond the moderate stage. It seems that similar troubles such as tendon rupture during exercise may be observed in upper extremities. In conclusion, it must be emphasized that the execution of more prudent rehabilitation are very important even in the time of biological agents mainly used for RA patients. To understand the rehabilitation for RA, follows are prepared. 1. To understand the impairments, disabilities and handicaps due to musculoskeletal disorders and the clinical usefulness of rehabilitation approach for them. 2. To advice the way of home-based exercise and protection for joint damage in daily life to RA patients. 3. To make the simple splint or insole for relieving the pain due to RA.

## MTE9

### Early diagnosis and treatment of systemic sclerosis

Hironobu Ihn

Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University

Conflict of interest: None

Systemic sclerosis (SSc), the focus of this lecture, is a generalized connective tissue disease that involves sclerotic changes in the skin and sometimes various other organ systems. Clinical outcomes have improved probably due to better management of the complications, but SSc is still considered to be incurable and diffuse cutaneous SSc carries high risk of fatality. In this lecture, I would like to talk about early diagnosis, clinical aspects, and treatment of this disease. I would also like to review recent clinical and basic topics of SSc.

## MTE10

### Management of glucocorticoid-induced osteoporosis

Satoshi Soen

Department of Orthopaedic Surgery and Rheumatology, Nara Hospital, Kinki University School of Medicine

Conflict of interest: Yes

A participant becomes available for the following issues by participating in this program. 1. You can understand epidemiology of glucocorticoid-induced osteoporosis 2. You can understand mechanisms of glucocorticoid action 3. You can understand effects of glucocorticoids on bone

and fracture risk 4. You can understand general measures for glucocorticoid-induced osteoporosis 5. You can understand assessments of fracture risk in glucocorticoid-induced osteoporosis 6. You can understand medication for glucocorticoid-induced osteoporosis

## MTE11

### Rheumatic diseases of the elderly

Yukitaka Ueki

Department of Rheumatology, Sasebo Chuo Hospital, Japan

Conflict of interest: Yes

As for an important disease, rheumatoid arthritis (RA), the vasculitis syndrome, the polymyalgia rheumatica (PMR), the dermatomyositis, and the systemic sclerosis, etc. are enumerated in the differential diagnosis of senior citizen's rheumatic diseases. Rheumatologists may more frequently encounter elderly patients with rheumatic diseases due to longer life expectancy than before. There are elderly onset arthritis patients whose rheumatoid factor and anti-CCP antibody were both negative at baseline. Differential diagnosis between seronegative RA and PMR is not easy and is still challenging for many rheumatologists. Moreover, serious complication and bone destruction were developed over the period of the short time of a part of senior citizen. The diagnostic and treatment are promptly requested. There are very important diseases with PMR, RA and microscopic polyangitis as senior citizen's unknown fever and the cause of the CRP high titer of an uncertain cause. with PMR, RA and microscopic polyangitis How to diagnosis and treat such diseases? In this seminar, those topics will be discussed among the participants.

## MTE12

### Orthopaedic surgery for rheumatoid arthritis in the biologic era

Keiichiro Nishida

Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

Conflict of interest: None

The clinical course of rheumatoid arthritis (RA) has dramatically improved over the past decade with new treatment strategies and introduction of biologic DMARDs (bDMARDs). The modern rheumatology have concentrated therapy on reducing inflammation, either locally or systemically, whereas patients' grovel assessment for disease control (PGA) is often the limiting factor for reaching ACR/EULAR criteria for remission, and the most significant determinants for the PGA has been reported to be pain. As causes of RA pain may vary between early and late disease, during and between inflammatory flares, and between different individuals, indication for surgical intervention for RA is often difficult to understand for rheumatologists. Pain of RA arises from multiple mechanisms, involving inflammation, peripheral and central pain processing, psychological distress, and structural change within the joint. The surgery for inflammatory pain of RA includes open or arthroscopic synovectomy for better disease control or prevention of further destruction. RA-related pain may be worsened by joint damage, which may be without inflammation or secondary to inflammatory. Surgeries for non-inflammatory pain include joint arthroplasty, arthrodesis, joint replacement. For patients in the third group without pain, surgery should be considered for cervical disorder with serious instability and neurological deficiency, elbow surgery in patients with bilateral involvement or ankylosis, distal radio-ulnar joint surgery for disturbed forearm rotation, tendon rupture and entrapment neuropathy. Increasing number of patients require surgery for finger deformity with cosmetic problem, even after the clinical and functional remission. With effective pharmacological inflammatory and non-inflammatory pain management, the most appropriate surgical procedure should be selected to improve the joint function which disturbing the ADL, or cosmetic problem.

## MTE13

### Respiratory infectious diseases under immunosuppressed condition

Naoki Hasegawa

Keio University Hospital



Conflict of interest: Yes

Immunosuppressive treatments, main therapeutic strategies against rheumatoid diseases, is known to be associated with increased risk of infectious events, while it is not proved that rheumatoid diseases themselves would be directly render them to be susceptible to infection. Although duration and intensity of each immunosuppressive treatment has been suggested to be related to the possibility of interference with cytokine function, inhibition of the second signal required for T-cell activation, leading to cellular rather than humoral immunity, while combination of them in most cases. In these situations typical clinical symptoms including fever and radiological findings are not necessarily observed, rather often associated with acute onset and rapid worsening, and delayed resolution, resulting in atypical clinical courses as well as laboratory measurements. Causative organisms are diverse ranging from protozoa, fungus to viruses. It is important to consider them in the connection with patients' backgrounds. Through case presentations we will discuss how to detect, evaluate and manage pulmonary infectious diseases during immunosuppressive treatment. Since there is no established measure to monitor immune functions controlling developing active infection, proper assessment of clinical status of each case such as, timely radiological evaluation comparing past films, and every efforts to obtain microbiological diagnosis with appropriate sampling of respiratory specimens as well as lung tissue, if necessary, using invasive procedures such as bronchoscopy, CT-guided biopsy and open lung biopsy. In addition to ordinary immunosuppressants such as steroid and methotrexate, recently available anti-TNF- $\alpha$  monoclonal antibodies in rheumatoid arthritis have been demonstrated to elevate chances to develop a series of infectious diseases. Furthermore it is important to manage infectious diseases with consideration for infection control and prevention.

#### **MTE14**

##### **Biological agents and its effects for recent changes of orthopaedic surgery in rheumatoid arthritis**

Yuichi Mochida

Center for Rheumatic Diseases, Yokohama City University Medical Center, Yokohama, Japan

Conflict of interest: Yes

The orthopaedic surgeries for rheumatoid arthritis (RA) are performed for pain relief, restoration of joint destruction, functional recovery, and improvement of quality of life MTX and other DMARDs come to be used widely for RA in Japan for approximately 15 years, additionally, the uses of the biologics are on the increase. As benefits of these changes of medication, the case which indicates the thinning of cortex bone, decreased bone mineral density at medullary bone, significant abnormality of joint alignment, and the giant geode or bone defect are remarkably decreasing. With the recent changes of joint destruction, there are many reports for the change of the number of the surgery of RA. We also realize increased cases of relatively low inflammatory joints with spur formation. On the other hand, the cases of severe destruction with high levels of inflammation are decreasing. This change may lead to differences of surgical technique between hospitals that may influence the postoperative results and complication rates. Whereas most of patients for RA surgery still have multiple organ complications with relatively long-term duration of disease. These cases are usually inhibited their immune system by updated medical treatment. It is very important to confirm the condition of each patient and we notice small abnormality and prevent complications. In this session, the reported change of the number of the surgery for RA and the recent changes of various joints will be discussed. Then the expected changes of surgical procedure, preoperative preparations, and the actual methods of prevention of perioperative complication in "the biologics era" will be debated.

#### **MTE15**

##### **Problems and therapeutic approaches for chronic musculoskeletal pain disorder**

Takahiro Ushida

Multidisciplinary Pain Center, Aichi Medical University

Conflict of interest: Yes

Pain is defined as an unpleasant sensory and emotional experience. Thus pain is always subjective and experience it in one's brain. Concerning about popular chronic musculoskeletal pain, medical providers usually pay careful attention to local organic issues (eg. Joint deformities etc.) and conventional bio-medical approaches (use anti-inflammatory drugs, nerve block, joint/spine surgery, etc.) are chosen for the treatment. Beside, recent chronic pain researches revealed that chronic pain condition is a complex condition and it obtains organic factors as well as psychosocial factors. Also brain neuroscience technology clarified that activation of pain associate default mode network and pain memory in patients with chronic musculoskeletal pain conditions. Multidisciplinary approaches are necessary for analyze chronic pain conditions and team of specialists in anesthesiology, psychiatry and orthopedics as well as the relevant paramedical professionals are essential to provide diagnosis and therapeutic options. Therapeutic strategy is based on a cognitive-behavioral approach, and patients are taught about methods for restoring physical function and coping with pain, mostly with drugs and exercise therapy, so that any pain present does not impair function and the patient can reintegrate into society.

#### **MTE16**

##### **How to treat with glucocorticoids**

Hisaji Oshima

National Hospital Organization, Tokyo Medical Center

Conflict of interest: None

Glucocorticoids have been used as one of a crucial agent for treatment of rheumatic diseases for more than two decades. Although it is well known that glucocorticoids should be used carefully because of a large number of serious adverse effects, an empirical use of glucocorticoids may be sometimes seen. In this section, scientific and evidence-based treatment with glucocorticoids will be clarified through discussion with attendances. Specifically, 1) variety of glucocorticoids and their characteristics, 2) routes of administration, 3) prevention and treatment of adverse effects, 4) interaction with other agents, 5) pregnancy and lactation, 6) limit of glucocorticoid treatments will be discussed.

#### **MTE17**

##### **Diagnosis and Treatment of the Idiopathic Inflammatory Myopathies**

Michito Hirakata

Medical Education Center, Keio University School of Medicine, Tokyo, Japan

Conflict of interest: Yes

The idiopathic inflammatory myopathies, polymyositis (PM) and dermatomyositis (DM) are a heterogeneous group of immune-mediated disorders characterized by proximal muscle weakness and involvement of various systemic organs. Especially, it has been noted that myositis-specific autoantibodies are closely associated with distinct clinical features and therefore significant tools for diagnosis, patient classification as well as predict of signs, symptoms of myositis, response to treatment, and prognosis. This session will review recent findings on clinical and laboratory aspects of PM/DM, including clinical significance of novel myositis-specific autoantibodies and comprehensive therapeutic strategies for intractable pathological conditions. Finally, the problems to be resolved as well as challenges in the patients with PM/DM will be discussed interactively, providing useful information in the daily practice of rheumatic diseases for the participants.

#### **MTE18**

##### **Essentials of radiologic imaging of chest diseases in patients with RA**

Takashi Hajiro

Department of Respiratory Medicine, Tenri Hospital, Nara, Japan

Conflict of interest: None

Patients with RA are frequently complicated with a wide variety of chest diseases, such as pulmonary infection (e.g. bacteria, tuberculosis, non-tuberculous mycobacterium, Pneumocystis), interstitial lung disease-

es, bronchiectasis, and drug-induced lung diseases. Accurate diagnosis and proper management for those complications are challenging for not only rheumatologists but also pulmonologists. Respiratory symptoms are non-specific with regard to diagnosis, therefore importance of chest imaging, particularly chest X-ray films, should be emphasized. It is recommended that rheumatologists have basic knowledge of analyzing chest imaging (chest X-ray films and CT scans). In this program, I would like to share essentials of imaging of chest diseases interactively and present actual chest X-ray films and CT scans commonly seen in patients with RA. Specifically, the audience will be able to learn about comparisons between chest images and anatomical structures, common nomenclature of description (e.g. airbronchogram, silhouette sign, ground glass opacity), systematic view of chest X-ray films and the right time to consult a pulmonologist. I am looking forward to having this interactive program with you.

## **MTE19**

### **MR Imaging of Rheumatic Diseases**

Tamotsu Kamishima

Faculty of Health Science, Hokkaido University

Conflict of interest: None

MR imaging (MRI) allows assessment of all the structures involved in rheumatoid arthritis (RA). MRI bone marrow edema appears to represent the link between joint inflammation and bone destruction. High MRI synovitis score are reported to predicts radiographic progression in patients in clinical remission/low disease activity. In this session, the practical skills of RA image interpretation will be provided according to RAMRIS for RA activity and damage. MR findings of RA involving other synovial spaces such as large joints and bursae will also be covered, because MR images of such anatomical structures may be obtained if there is a specific clinical indication. In addition, MR images of complication of RA (secondary osteoarthritis, tendon rupture, and septic arthritis) and differential diagnosis of RA (ankylosing spondylitis, psoriatic arthritis, SAPHO syndrome, RS3PE syndrome, and spondyloarthropathy) will be demonstrated in this session.

## **MTE20**

### **Management of liver dysfunction in patients with collagen diseases**

Akio Ido

Digestive and Lifestyle Diseases, Kagoshima University Graduate School of Medical and Dental Sciences

Conflict of interest: Yes

Collagen diseases are systemic inflammatory disorders that often exhibit liver involvement due to autoimmune mechanisms or drugs. The cause and degree of liver involvement vary with each collagen disease. Liver dysfunction is found in approximately 40% of patients with rheumatoid arthritis (RA), and is primarily caused by anti-rheumatic drugs. Conversely, non-specific reactive hepatitis, which is characterized by non-specific lymphocyte infiltration within portal areas, is due to RA activity itself. Between 30 and 60% of patients with systemic lupus erythematosus (SLE) develop liver dysfunction, the causes of which include SLE itself, fatty liver resulting from steroid administration, and drugs. Autoimmune hepatitis, which is characterized by interface hepatitis and an increase in serum ALT and IgG, is often found in patients with SLE. Liver dysfunction is seen in 10-50% of patients with Sjogren's syndrome, and primary biliary cirrhosis is a well-known complication of this condition. Hepatitis B virus (HBV) reactivation related to immunosuppressive therapy has recently been increasing in patients with hematological malignancies and rheumatological diseases. All of these patients should therefore be screened for hepatitis B surface antigen (HBsAg), and testing for hepatitis B core antibody (HBcAb) and HBsAb should be performed in HBsAg-negative patients who receive immunosuppressive therapy for rheumatological disease. Prophylaxis with nucleoside analogs is essential for preventing HBV reactivation in HBsAg-positive patients. In contrast, HBsAg-negative patients who are HBcAb- and/or HBsAb-positive should be monitored monthly for increases in serum HBV DNA during chemotherapy and for 12 months afterward.

## **MTE21**

### **How to manage the refractory RA patients?**

Atsushi Kawakami

Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences

Conflict of interest: Yes

Prognosis of RA is improved after introduction of biologic DMARDs (bDMARDs) since the proportion of RA patients in clinical, functional and structural remission is proved to increase. However, some of the RA patients still remain in refractory toward remission; such as 1. RA patients refractory toward DMARDs including bDMARDs 2. RA patients with some complications 3. Elderly active RA patients or advanced RA patients. Regarding to 1., RA patients with high disease activity are, in general, refractory. Even in the use of bDMARDs, the clinical response at 3 months is reported to associate with clinical status at 1 year. In case of TNF inhibitors, high titer of RF or ACPA at baseline may associate with unfavorable response. Some investigations have found the association of serum/plasma cytokines such as TNF-alpha, IL-6 or sIL-6R with clinical response of bDMARDs. By using the above-mentioned indices, appropriate choice/change of DMARDs are recommended through considering the clinical response at 3-6 months. Regarding to 2., the presence of infection, pulmonary complications, renal disturbance or HBV carrier/HBsAg/HBsAb/HBcAb/HBVDNA become to be the limitation factors toward the choice of DMARDs. The guidelines or recommendations published by JCR/ACR/EULAR are quite useful to select the DMARDs in such cases. Regarding to 3., in case of elderly RA patients, the similar caution is necessary to select DMARDs as 2. In general, the introduction of remission is difficult in advanced RA patients, therefore, the target may be changed to low disease activity. In this MTE, the above-mentioned items will be discussed.

## **MTE22**

### **Refractory systemic lupus erythematosus (SLE)**

Tomonori Ishii

Division of Hematology and Rheumatology, Tohoku University Hospital

Conflict of interest: Yes

Most recent studies have reported 5-year survival rates of 90% or more, which would seem to suggest a good prognosis of SLE. However, some Western studies have shown 20-year survival rates of around only 70%. About one-third of the deaths in patients with SLE are attributable to difficult control of SLE itself, while other causes of death include infections, vascular diseases, and malignancies. Treatment with glucocorticoids (GC) is strongly associated with the development of infections and vascular disorders. Fatal conditions in patients with refractory SLE include severe lupus nephritis, CNS manifestations, pulmonary alveolar hemorrhage, and pulmonary hypertension. There is, however, a lack of adequate evidence for appropriate treatment of these conditions. In this situation, the essential principles of treatment are 1) Precise understanding of the present illness: Clinicians should try and obtain as much useful information about the patient as possible before starting treatment 2) Selection and use of proper assessment methods: Clinicians should determine appropriate methods to estimate the treatment effects before starting therapy. 3) Selection of the most effective treatment method: Clinicians can provide treatment based on the standard treatment protocol for lupus nephritis, since the protocol is supported by the highest level of evidence. 4) Proper execution of the treatment plan: It is important to optimize treatment by predicting the patient's response to therapy. This strategy would help clinicians individualize the treatment plan, especially for the case of patients who do not respond to standard therapy. On the other hand, novel treatment approaches are needed for patients with refractory SLE or those who are difficult to control with low-dose GC therapy. Currently, many biological agents for the treatment of SLE are under investigation in clinical trials, offering hope for improvement of the clinical outcomes.

## Specified Workshop

### SW1-1

#### Hydroxychloroquine as a standard treatment in lupus

Masato Okada, Chisun Min, Mitsumasa Kishimoto  
Immuno-Rheumatology Center, St. Luke's International Hospital, Tokyo, Japan

Conflict of interest: Yes

Hydroxychloroquine is a major pharmaceutical intervention in the treatment of systemic lupus erythematosus in the world. It is expected to be available as a standard treatment of lupus in Japan in the near future. It is imperative for all the rheumatologists to be well-versed in the expected efficacy and necessary monitoring.

### SW1-2

#### Hydroxychloroquine (HCQ) and CLE

Akiko Tanikawa<sup>1</sup>, Masayuki Amagai<sup>1</sup>, Tsutomu Takeuchi<sup>2</sup>  
<sup>1</sup>Department of Dermatology, Keio University School of Medicine, Tokyo, Japan, <sup>2</sup>Department of Rheumatology, Keio University School of Medicine, Tokyo, Japan

Conflict of interest: None

For decades, Hydroxychloroquine (HCQ), an antimalarial drug, has been used to treat systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (CLE) with excellent results. The disease mainly affects young women, who report hugely negative effects on their QOL as a result of the refractory skin manifestations. Although HCQ is the first-line therapy in the management of SLE and CLE around the world, in Japan the drug is not available. The standard therapeutic alternative to HCQ for treating CLE in Japan is topical therapy followed by prednisolone (PSL) only or in combination with an immunosuppressant. The recurrence of lesions when only low doses of PSL are administered leads to long-term use of corticosteroids and a host of concomitant adverse events. In this lecture, we summarize 50 cases of HCQ from our clinical experience, and discuss the safety, efficacy, and side effects of the drug using clinical images.

### SW1-3

#### The innate immune mechanism of action of hydroxychloroquine

Hajime Kono<sup>1</sup>, Yoshitaka Kimura<sup>1,2</sup>, Daisuke Tsukui<sup>1</sup>, Mai Okubo<sup>1</sup>, Kurumi Asako<sup>1</sup>, Hirotohi Kikuchi<sup>1</sup>, Zen-ichiro Honda<sup>1,4</sup>, Toshihiro Nanki<sup>1,3</sup>, Akiko Okamoto<sup>1</sup>  
<sup>1</sup>Department of Internal Medicine, Teikyo University School of Medicine, <sup>2</sup>Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, <sup>3</sup>Teikyo Academic Research Center, Teikyo University School of Medicine, <sup>4</sup>The Division of Life Sciences, Ochanomizu University Graduate School of Humanities and Sciences

Conflict of interest: Yes

Hydroxychloroquine was first developed as an anti malarial medicine, later used for the treatment of rheumatoid arthritis and lupus erythematosus. Hydroxychloroquine improves not only cutaneous and musculoskeletal manifestations, but also overall survival of lupus patients. One of the mechanisms of hydroxychloroquine of improving lupus is the inhibition of activation of Toll like receptors (TLRs). The inhibitory activity has been attributed to the inhibition of endosomal acidification, because acidic pH is a prerequisite of endosomal TLR activation. In addition, it was shown that the interaction between chloroquine and nucleic acids affected TLRs' conformation and availability for TLR binding sites. Self nucleic acids are usually destroyed quickly outside of the cell. In the presence of anti DNA antibodies or DNA binding proteins such as LL37 or HMGB1, self nucleic acids are protected from nucleases and delivered to endosome via Fc receptors which then activates TLRs. Activation of TLRs on plasmacytoid DC leads to production of type I interferons, which is an important signature of disease activity of lupus erythematosus. Another proposed mechanism of action of hydroxychloroquine is interference with normal physiological functions of subcellular compartments that rely on an acidic milieu. Antigen presentation relies on the

endosomal acidification and can be inhibited by hydroxychloroquine, which increases the pH of lysosome and endosome. In addition, hydroxychloroquine suppresses autophagy of B and T cells, which can modulate the inadequate autophagic activity of lupus lymphocytes. Interestingly, a case-control study aiming to identify factors predictive of infectious complications reported that SLE patients treated with antimalarial agents had a lower risk of major infections. This makes hydroxychloroquine a unique medicine, which has a double action of immunosuppression of inadequate autoimmune response and immune activation toward infection.

### SW1-4

#### Hydroxychloroquine and chloroquine retinopathy

Kei Shinoda, Soichi Matsumoto  
Teikyo University School of Medicine, Tokyo, Japan

Conflict of interest: Yes

Chloroquine (CQ) retinopathy, as retinopathy characterized with bilateral macular lesion, visual loss, and visual field deficit, associated with long-term use of CQ or hydroxychloroquine (HCQ), was first reported by Hobbs et al in 1959. Although it is rare, it may progress even after cessation of the drug, and no effective treatment exists. Therefore importance of early detection has been emphasized in many reports and screening regimen has been discussed considering cost effectiveness. Long-term use more than 5 years, dosage of the drugs, elderly person, and other diseases such as renal or liver dysfunction, and retinal disease has been pointed out as a risk factor for the development of the retinopathy. The dose that can be a risk varies between two drugs; the daily dose is >3.0mg/kg for CQ, and >6.5mg/kg for HCQ, and the cumulative dose is >460g for CQ, and >1000g for HCQ. The incidence is reported to be about 0.5% in the long-term use more than 5 years. The retinopathy is characterized by ophthalmoscopically detectable retinal changes when advanced, such as ring-shaped atrophy surrounding macula, so-called 'bull's eye'. Functionally, it causes sensitivity loss of the central visual field, vision loss, and so on. Ophthalmic examination before drug administration and regular ophthalmic examination after administration are important for early detection. The interval of once a year if there is no above-mentioned risk factors, otherwise a shorter is desirable. Specifically, slit lamp microscopy, ophthalmoscopy, and testing for visual acuity, the central visual field, and color vision should be performed. Further, when ocular abnormality is suspected, the more precise fundus inspection such as optical coherence tomography and fundus autofluorescence would be helpful to detect subtle abnormality with accuracy. I will show these ophthalmic findings and propose a flow of ophthalmic screening with taking the prevalence situation of the testing equipment in Japan into account.

### SW1-5

#### A phase 3 trial of hydroxychloroquine in Japan

Naoto Yokogawa<sup>1,7</sup>, Fukumi Furukawa<sup>2,7</sup>, Hikaru Eto<sup>3,7</sup>, Akiko Tanikawa<sup>4,7</sup>, Takaharu Ikeda<sup>2,7</sup>, Toshiya Takahashi<sup>6</sup>, Kazuhiko Yamamoto<sup>5,7</sup>  
<sup>1</sup>Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, Japan, <sup>2</sup>Department of Dermatology, Wakayama Medical University, <sup>3</sup>Department of Dermatology, St. Luke's International Hospital, <sup>4</sup>Department of Dermatology, Keio University School of Medicine, <sup>5</sup>Department of Allergy and Rheumatology, The University of Tokyo, <sup>6</sup>Sanofi K.K., <sup>7</sup>Japanese Hydroxychloroquine Study Group

Conflict of interest: None

A double-blind, randomized, baseline-controlled, phase 3 trial using a placebo (PLA) as the reference was conducted to assess the efficacy and safety of Hydroxychloroquine (HCQ) in SLE or CLE patients (age $\geq$ 18) with active LE-specific skin lesions, Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score $\geq$ 4, without fluctuations $<$ 20%. It consists of double-blind (HCQ or PLA in a 3: 1-16 weeks), single-blind (HCQ-36 weeks), and follow-up (3 weeks). Primary endpoint was a change in CLASI activity score from baseline to 16 weeks. Skindex29, 7-point scale global assessment (GA) of skin by patient, 5-point scale central photo evaluation, were assessed and, based on them 7-point scale GA of skin was scored by investigator. In SLE, fatigue VAS, pain VAS, RAPID 3, and focused BILAG were assessed. 103

patients were randomized and 72 in HCQ/HCQ, 24 in PLA/HCQ were analyzed for efficacy. The change in CLASI activity score at 16 weeks in HCQ/HCQ was  $-4.6 \pm 6.4$  ( $p < 0.001$ ) and that in PLA/HCQ was  $-3.2 \pm 4.5$  ( $p = 0.002$ ). That in PLA/HCQ improved after switching to HCQ from 16 to 32 weeks (PLA/HCQ  $-2.4 \pm 4.7$ , HCQ/HCQ  $-0.8 \pm 2.7$ ) and continued until 52 weeks. Skindex29 improved significantly from baseline to 16 weeks in HCQ/HCQ. The ratio of “ $\geq$ slightly improved” by GA of skin by patient, “ $\geq$ improved” by central photo evaluation, and “ $\geq$ improved” by GA of skin by investigator, were 72.9%, 59.4%, and 51.4% in HCQ/HCQ and 45.5%, 31.8%, and 9.1% in HCQ/HCQ from baseline to 16 weeks. In SLE (56.3%), fatigue VAS, pain VAS, and RAPID3 improved significantly from baseline to 16 weeks in HCQ/HCQ. Active musculoskeletal system (A-C) defined by BILAG improved to be one letter down in 42.1% of HCQ/HCQ to 16 weeks. Adverse events (AEs), serious AEs, related AEs to HCQ in 52-Week HCQ administration arm ( $n = 77$ ) were 97.4%, 10.4%, 32.5% and frequent related AE exceeding 10% was only diarrhea. Most AEs were mild or moderate, although 2 cases of severe drug eruptions were observed in HCQ/HCQ.

## SW2-2

### Infliximab

Takao Koike

NTT Sapporo Medical Center

Conflict of interest: Yes

Infliximab (IFX) is the first anti-TNF $\alpha$  antibody agent which specifically neutralizes human TNF $\alpha$ . An estimated over two million patients have been treated with IFX worldwide since its first approval in US in 1998. In a few years after marketing, increased risk of tuberculosis (TB) or opportunistic infections associated with IFX, which were rarely observed in clinical trials, began to be reported. In Japan, IFX was approved for Crohn's disease in 2002, followed by RA in 2003. As an approval condition for RA, large post-market surveillance (PMS) was mandated to monitor prospectively all adverse drug reactions (ADRs) for six months in all RA patients treated with IFX. Japan College of Rheumatology (JCR) organized PMS committee to supervise the conduct of the study providing directions and guidance, and shared the findings with doctors in clinical settings. The results of the PMS with 5,000 cases revealed that 1) the safety profiles in Japanese patients were similar to those in Western countries, 2) most frequent serious ADRs were infections, of which independent risk factors were elderly, accompanying respiratory disease and concomitant use of oral glucocorticoids, 3) no TB cases were observed in patients who had received prophylactic anti-TB drugs and incidence of TB decreased with increased use of anti-TB drugs, 4) pneumocystis jiroveci pneumonia cases that was hardly reported in clinical trials were observed. IFX was subsequently approved for several other autoimmune diseases and PMS was conducted in most of those approved indications as well. This is the first PMS study enrolled all RA patients who received biologics in Japan. The interim/final reports were submitted to JCR and provided important information for JCR to develop the guidelines for the use of anti-TNF $\alpha$  agents for RA. The study has also contributed significantly to the PMS of subsequent biologics after IFX.

## SW2-3

### Etanercept

Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: Yes

Etanercept was launched in 2005 as the second anti-TNF agent approved for RA. Since the safety profile of anti-TNF agents in Japanese patients was not well defined at that time, all case PMS study was conducted as well as that of infliximab launched in 2003. A total 14,421 cases were registered from March 2005 to April 2007, and finally analysis was conducted in 13,894 cases for safety profile and 13,023 cases for efficacy profile. Baseline profile includes 81.4% female, average age 58.1 years old, average body weight 53.2kg, and average disease duration 9.4 years. 57.1% had any comorbid diseases, 29.1% received prophylaxis for tuberculosis. 13.5% had history of infliximab infusion and 55.9% has concomitant use of methotrexate. Efficacy analysis demonstrated that

average DAS28 improved from 5.87 to 3.77 after 24 weeks. At 24 weeks, 31.6% achieved EULAR good response and 18.9% achieved clinical remission. Baseline characteristics related to remission were gender, age, Stage, Class, dose of methotrexate and baseline DAS. Safety analysis showed that 26.8% of cases experienced any adverse reactions and 4.6% had serious adverse events. Among those, infection was the most prevalently reported in 1,206 cases (8.68%), and severe infection was noted in 334 cases (2.4%), included pneumonia (174 cases, 1.25%), Pneumocystis pneumonia (25 cases, 0.18%) and interstitial pneumonia (81 cases, 0.58%). Patients without concomitant methotrexate were higher risk for side effects. Concomitant non-serious infection, use of corticosteroid and history or concomitant pulmonary diseases had higher hazard risk for serious infection. Standardized mortality ration was also calculated and was 1.46 (1.15 - 1.84) by 24 weeks ITT analysis. Etanercept all case PMS contributed largely for the etanercept use in the daily practice, and this PMS was conducted in the largest number of cases among all-case PMR of biologics, and evaluated the disease activity using DAS 28 for the first time.

## SW2-4

### Tocilizumab

Tsutomu Takeuchi

Keio University School of Medicine, Tokyo, Japan

Conflict of interest: Yes

Tocilizumab (TCZ) is used for rheumatoid arthritis (RA) patients worldwide. TCZ is recommended for RA patients not only who have inadequate response to TNF inhibitors as a 2<sup>nd</sup> line treatment but also who have insufficient efficacy to DMARDs as a 1<sup>st</sup> line of biologic agent in Japanese College of Rheumatology (JCR), EULAR recommendations and ACR guideline. There are concerns about several adverse events such as severe infections which were thought to be specifically induced by blocking IL-6, when TCZ was initially developed. Therefore, the ministry of health, labor and welfare, JCR and Chugai conducted the post marketing surveillance (PMS) for all of the TCZ patients following the PMS for infliximab and etanercept. Baseline characteristics of TCZ patients were apparently different from those of infliximab and etanercept patients. The background of TCZ patients were established RA (mean disease duration; 10.2 years), intolerant to MTX (because of comorbidities such as interstitial lung diseases), and inadequate response to TNF inhibitors. After the first report, the second and the third interim reports were published continually. The final data of 7,901 patients published in 2013 enabled us to analyze larger number of patients in more detail. Additionally, the long term data (3 year follow-up data) which observed 5,501 patients with TCZ treatment were published in 2014. These PMS results with lots of evidence of TCZ contributes to reducing almost all of the concerns that physicians potentially had for the IL-6 inhibitor, which can result in more safe prescription of TCZ. The PMS data of TCZ are highly recognized by global physicians as they reflect current RA treatment in Japan.

## SW2-5

### Analysis of benefit and risk balance of adalimumab in the all-cases postmarketing surveillance program in Japan

Masayoshi Harigai<sup>1,2</sup>

<sup>1</sup>Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, <sup>2</sup>Department of Rheumatology, Tokyo Medical and Dental University Hospital

Conflict of interest: Yes

All-cases postmarketing surveillance program for adalimumab (ADA) was implemented from 2008 to 2010 and enrolled 7740 patients with RA who used ADA after its launch into the market. Safety and effectiveness data up to week 28 and 24, respectively, were already reported (Modern Rheumatology 2011 and 2013). Baseline characteristics of the enrolled patients were as follows: female, 83%; mean age, 60 years old; mean disease duration, 11 years; mean DAS28-ESR, 5.2; comorbidity, 62%; previous use of biologics, 42%. Concomitant MTX and glucocorticoid (GC) were used in 71% and 67%, respectively. Adalimumab was administered at 40mg every two weeks in 96% of the patients and

drug retention rate at week 24 was 71%. Adverse drug reactions (ADRs), serious ADRs and serious infections were reported from 24%, 4.5% and 2.4%, respectively. Reported number of patients with ADRs of interest were 9 with active tuberculosis (0.1%), 26 with *Pneumocystis jirovecii* pneumonia (0.3%), 52 with interstitial pneumonia (0.7%), 13 with malignant neoplasm (0.2%), 317 with injection site reaction (4.1%). Thirty-one patients died during the observation period and standardized mortality ratio (SMR) was 0.89 with 95% confidence interval of 0.61 – 1.26. Older age, use of PSL >5 mg/day and presence of pulmonary comorbidity were identified as significant risk factors for both serious infections and serious respiratory infections. Mean DAS28-ESR significantly decreased from 5.2 at week 0 to 3.8 at week 24. Multivariate analysis indicate that lower DAS28-ESR, biologic-naïve, concomitant use of MTX, non-concomitant use of GC, and less advanced Steinbrocker's stage and class were significant predictors of achieving DAS28-ESR  $\leq$ 3.2 at week 24. Recent analysis revealed that changes in characteristics of the patient over time was associated with better safety and effectiveness profile of the drug during the PMS. Benefit-risk balance of ADA in clinical setting will be discussed in this workshop.

## SW2-6

### Abatacept

Yoshiya Tanaka<sup>1</sup>, Masayoshi Harigai<sup>2</sup>, Naoki Ishiguro<sup>3</sup>, Shigeko Inokuma<sup>4</sup>, Junnosuke Ryu<sup>5</sup>, Syuji Takei<sup>6</sup>, Tsutomu Takeuchi<sup>7</sup>, Hisashi Yamanaka<sup>8</sup>, Takao Koike<sup>9</sup>

<sup>1</sup>The First Department of Internal Medicine, School of Medicine, University of Occupational & Environmental Health, Japan, <sup>2</sup>Tokyo Medical and Dental University, Graduate School of Medical and Dental Sciences, Tokyo, Japan, <sup>3</sup>Nagoya University, Graduate School & Faculty of Medicine, Nagoya, Japan, <sup>4</sup>Japanese Red Cross Medical Center, Tokyo, Japan, <sup>5</sup>Nihon University School of Medicine, Tokyo, Japan, <sup>6</sup>Kagoshima University School of Health Science, Kagoshima, Japan, <sup>7</sup>Keio University School of Medicine, Tokyo, Japan, <sup>8</sup>Tokyo Women's Medical University, Tokyo, Japan, <sup>9</sup>Sapporo Medical Center NTT EC, Sapporo, Japan

Conflict of interest: Yes

Abatacept (ABT) is a soluble recombinant fusion protein in which the extracellular domain of human CTLA-4 and the Fc domain of human IgG1 are fused together. It is said to exhibit strong affinity for CD80/CD86 on the surface of antigen-presenting cells and to inhibit T-cell activation and suppress pro-inflammatory cytokine production and inflammatory effector cell activation by selectively down-regulating the T-cell costimulatory signal. In July 2010 ABT was approved in Japan as the fifth biologic for rheumatoid arthritis (RA). In May 2013 we completed post-marketing surveillance (PMS) of all patients treated with ABT. The target number was 4000 patients, and 24 weeks was the observation period. Safety and effectiveness were analyzed in 3985 patients. Age was 61.3 years; RA duration was 10.3 years. Stage III and IV 63.1% of patients; Class III and IV 24.9%; and 69.1% had been switched from another biologics. Methotrexate (MTX) 7.11 mg/week and corticosteroid 5.0 mg/day were used concomitantly in 67.0%, and 63.3%, respectively. The RA complication rate was 69.7%, and they were established patients. The incidence of adverse drug reactions (ADRs) was 15.4%: serious ADR (S-ADR) 2.5%, S-infection 1.0%, S-hypersensitivity 0.1%, autoimmune disease 0.3% malignant tumor 0.2%, interstitial pneumonia 0.3%, pancytopenia 0.2%, tuberculosis 0.03%, demyelinating disease 0.03%, psoriasis 0.2%. There were no differences in known ADRs from other-mechanism biologics. The continuation rate was 79.3%, and at 24 weeks the DAS28 CRP remission rate was 26.5%, and low disease activity 37.8%, and thus disease activity had improved over baseline. The effects of MTX, and switching from other biologics or corticosteroids were pointed out in the results of other biologics. In the workshop, we will review safety, effectiveness, and multivariate analysis data for proper use of ABT.

## SW2-7

### Iguratimod — From a report covering 24 weeks of the post marketing surveillance of all-patients —

Naoki Ishiguro<sup>1</sup>, Kazuhiko Yamamoto<sup>2</sup>

<sup>1</sup>Department of Orthopaedics and Rheumatology, Nagoya University, School of Medicine, Nagoya, Japan, <sup>2</sup>Department of Allergy and Rheu-

matology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Conflict of interest: Yes

MTX is currently an “anchor drug” for the early treatment of rheumatoid arthritis (RA). Even if treatment is started at a sufficient dose of MTX, 20 - 40% of patients do not respond well. If the treatment goals are not achieved, the concomitant addition of other DMARDs or biological preparations may be required. Iguratimod (IGU) is a new synthetic disease-modifying anti-rheumatic drug (DMARD) that a domestic phase III study has shown to be noninferior to salazosulfapyridine when provided as monotherapy. Its addition combined effect in patients who have had an inadequate response to MTX therapy (MTX-IR) has been verified. Based on these data, IGU has been approved in the context of the current treat-to-target (T2T) approach. The post marketing surveillance of all-patients treated with IGU was performed after its launch in September 2012, in which the patients' background, status of combination with DMARDs, continuation rate, as well as status of occurrence of adverse reactions and risk factors as the principal items of investigation, and the disease activity and improvement rating in terms of safety and efficacy for elderly, low-body-weight patients and the presence or absence of combination of MTX were analyzed in 2737 patients enrolled before April 14, 2013. We report the statistical results over 24 weeks of the all-patient investigation.

## SW2-8

### Tofacitinib

Tatsuya Atsumi

Hokkaido University Graduate School of Medicine, Sapporo, Japan

Conflict of interest: Yes

Tofacitinib is an oral, small-molecule Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis. The drug interferes with the JAK-STAT signaling pathway, which transmits extracellular information into the cell nucleus, influencing DNA transcription. A series of studies have shown its dramatic efficacy for Japanese patients with RA, leading to the approval for its daily clinical practice. However, some adverse events including Herpes Zoster and malignancies were reported. PMS, conducted by JCR, was designed to prove its efficacy and safety in real-world Japanese patients. The observation period, 3 years, was longer compared with that in previous PMS for anti-TNF reagents. In addition, control group, “RA patients on bDMARDs” was defined and registered as well in this PMS. The PMS on Tofacitinib has been still on the patient recruitment. In this review, the latest collection of the data from the PMS will be presented.

## International Concurrent Workshop Clinical

### ICW-C1-1

#### The value of serum interleukin-6 before 1<sup>st</sup> biologics are predicted to clinical response in the patients of rheumatoid arthritis one year after the treatment

Yuya Takakubo, Yasushi Naganuma, Hiroharu Oki, Suran Yang, Akiko Sasaki, Tomoyuki Hirayama, Yasunobu Tamaki, Daiichiro Takahara, Junichi Okamoto, Hiroshi Orui, Kan Sasaki, Michiaki Takagi  
Department of Orthopaedic Surgery, Yamagata University Faculty of Medicine, Yamagata, Japan

Conflict of interest: None

[Objectives] Biologics (BIO) improve remarkably the treatment of RA, however 20–30 % of RA patients using BIO are nonresponders or show only minor improvement. Recently, significant relation between concentration of serum cytokines and responsiveness of RA treatments has been reported. We investigate the relationships of it before taking first BIO and the change of disease activity in our series. [Methods] Forty-three patients in BIO naive cases (infliximab 16 cases, etanercept 14, tocilizumab 10, adalimumab 3) were examined the concentration of serum TNF-alpha, IL-1 beta, IL-6 before receiving first BIO by ELISA. They are estimated the transition of DAS28/CRP score (4) and CDAI one year after first BIO. They are 7 men and thirty-six women. Their mean age is 54 years (range 32-75), mean duration of RA affliction was 7.5 years (1-22). [Results] The mean concentration of serum TNF-alpha and IL-1 beta, IL-6 was 15.2 pg/ml; 10.6; 33.5 before first BIO, respectively. The mean CRP levels, DAS28-CRP (4) and CDAI were 3.0 mg/dl, 4.9 and 25.5 before first BIO, which improved as 0.8 mg/dl, 3.2 and 11.2 one year after first BIO, respectively. EULAR response criteria were used, and there was a good response in twenty-seven patients (63 %), a moderate response in ten (23 %) and no response in six (14 %), respectively, during the treatment period starting at the commencement of the BIO and one year after. Only the value of serum IL-6 was significantly related to the results of EULAR response and CRP before first BIO ( $p < 0.05$ ). [Conclusions] The value of serum IL-6 before receiving BIO seems to have the potential marker for predicting the response of BIO treatment in RA patients.

### ICW-C1-2

#### Prognostic factors toward rapid radiographic progression in patients with rheumatoid arthritis in clinical practice: a Japanese multicenter, prospective longitudinal cohort study for achieving treat to target strategy

Tomohiro Koga<sup>1</sup>, Akitomo Okada<sup>2</sup>, Atsushi Kawakami<sup>1</sup>, Takaaki Fukuda<sup>3</sup>, Toshihiko Hidaka<sup>4</sup>, Tomonori Ishii<sup>5</sup>, Yukitaka Ueki<sup>6</sup>, Takao Kodera<sup>7</sup>, Munetoshi Nakashima<sup>2</sup>, Yuichi Takahashi<sup>8</sup>, Seiyu Honda<sup>9</sup>, Ryu Watanabe<sup>5</sup>, Hiroshi Okuno<sup>10</sup>, Mami Tamai<sup>11</sup>, Kiyoshi Aoyagi<sup>12</sup>, Katsumi Eguchi<sup>13</sup>

<sup>1</sup>Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, <sup>2</sup>Japanese Red Cross Nagasaki Genbaku Hospital, Japan, <sup>3</sup>Kurume University Medical Center, Fukuoka, Japan, <sup>4</sup>Zenjinkai Shimin-no-Mori Hospital, Japan, <sup>5</sup>Department of Hematology and Rheumatology, Tohoku University Hospital, Japan, <sup>6</sup>Sasebo Chuo Hospital, Japan, <sup>7</sup>Tohoku Pharmaceutical University Hospital, Japan, <sup>8</sup>Yu Family Clinic, Japan, <sup>9</sup>Kurume University School of Medicine, Japan, <sup>10</sup>Department of Orthopaedic Surgery, Tohoku University Hospital, Japan, <sup>11</sup>Center for Health & Community Medicine, Nagasaki University, Japan, <sup>12</sup>Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, <sup>13</sup>Sasebo City General Hospital, Nagasaki, Japan

Conflict of interest: None

[Objectives] To determine prognostic factors of rapid radiographic progression (RRP) in patients with rheumatoid arthritis (RA) in clinical practice for achieving treat to target strategy. [Methods] We performed a Japanese multicenter prospective study on biological disease-modifying antirheumatic drugs (bDMARDs)-naïve 942 RA patients with moderate to high disease activity or with radiographic bone erosion, treated with conventional synthetic DMARDs (csDMARDs) at study entry. We ob-

served longitudinally these patients for 1 year and assessed DAS28-ESR every 3 months. bDMARDs were introduced if disease activity is not controlled by csDMARDs alone and we observed these patients for additional 1 year after introduction of bDMARDs. RRP was defined as yearly progression of modified total Sharp score (mTSS)  $> 3.0$ . Furthermore, we divided into two groups based on disease duration ( $< 3$  years or  $\geq 3$  years) and examined for subgroup analysis. [Results] RRP was found in 9.6% of patients. Multiple step-wise regression analysis revealed that introduction of bDMARDs (OR=0.12, 95% CI 0.03 to 0.55,  $p=0.006$ ), time-integrated DAS28-ESR during 1 year (OR=1.04, 95% CI 1.01 to 1.06,  $p=0.002$ ) and CRP at baseline (OR=1.24, 95% CI 1.07 to 1.43  $p=0.005$ ) are independent variables to predict the development of RRP. In subgroup analysis, we found that the protective effect of bDMARDs toward RRP is only evident in RA patients disease duration  $< 3$  years. [Conclusion] RRP in RA patients treated with DMARDs is closely associated with persistent disease activity or introduction of bDMARDs. Prognostic factors of RRP are different according to the disease duration.

### ICW-C1-3

#### The impact of physical function on patient global assessment in rheumatoid arthritis

Tatsuo Watanabe, Toshihisa Kojima, Nobunori Takahashi, Koji Funahashi, Shuji Asai, Toki Takemoto, Kenya Terabe, Yutaka Yoshioka, Nobuyuki Asai, Naoki Ishiguro  
Department of Orthopaedic Surgery, Nagoya University School of Medicine, Nagoya, Japan

Conflict of interest: None

[Objectives] In 2011 ACR/EULAR Boolean-based definition of remission in RA, patient global assessment (PGA) is often the limiting factor for reaching remission. The main determinants for the PGA are pain, function, and number of swollen joints. Physical functions will affect clinical remission. Given the tight correlation between physical function and loss of social and economic opportunities, as well as clinical remission, functional remission is also an important goal. The impact of physical function on PGA was investigated. [Methods] 512 RA patients at Nagoya University Hospital were enrolled in this study. Physical function was assessed using Health Assessment Questionnaire (HAQ), disease activity DAS28-CRP, and PGA 0-10 visual analog scale. [Results] Patients were primarily women (81.4%). Mean age was 60.3 years, disease duration 13.0 years, HAQ-DI 0.67, and DAS28-CRP 2.37. PGA had a most strong correlation with the HAQ-DI in the components of the DAS28-CRP ( $r=0.395$ ). Of the patients who were in functional remission (HAQ-DI  $\leq 0.5$ ), 50.3% fulfilled PGA 0 or 1, of the patients whose HAQ-DI  $> 0.5$ ; only 16.0% fulfilled PGA 0 or 1. 277 patients fulfilled swollen joint count, tenderness joint count, and CRP 1 or less. 46.2% fulfilled Boolean-based remission, and 53.8% fulfilled three of four Boolean criteria except PGA. Mean HAQ-DI was the former 0.19, the latter 0.67, which showed a significant difference. By ROC analysis of the 277 patients fulfilled swollen joint count, tenderness joint count, and CRP 1 or less, cut off value that satisfies PGA 0 or 1 was HAQ-DI=0.18. Multivariate analysis revealed that disease duration independently predicted HAQ-DI  $\leq 0.18$ . [Conclusion] Physical function had an impact on PGA. Cut off value that satisfies PGA 0 or 1 was HAQ-DI =0.18, which was stringent than the HAQ remission ( $\leq 0.5$ ), and difficult for established RA cases to satisfy.

### ICW-C1-4

#### Correlation of Disease Activity with Arterial Stiffness in Rheumatoid Arthritis Patients

Anna Ariane<sup>1</sup>, Harry Isbagio<sup>1</sup>, Dono Antono<sup>2</sup>

<sup>1</sup>Rheumatology Division, Departement of Internal Medicine, Faculty of Medicine University of Indonesia, Cipto Mangunkusumo Hospital, Indonesia, <sup>2</sup>Cardiology Division, Departement of Internal Medicine, Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo Hospital, Indonesia

Conflict of interest: None

**Objectives:** Rheumatoid arthritis (RA) is a chronic progressive inflammatory disease related to increase in morbidity due to joint deformity

and increase in mortality due to cardiovascular event. One of cardiovascular event predictor is local arterial stiffness (AS). Inflammatory process in RA that is reflected on disease activity score (DAS) 28 calculated by c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) suspect to be related with AS. This study was aimed to find correlation between disease activity score and arterial stiffness in RA patients. **Methods:** a cross sectional study was conducted in Rheumatology outpatient clinic in Cipto Mangunkusumo Hospital between April-May 2014. Arterial stiffness was measured by carotid artery ultrasound using echotracking technique to get pulse wave velocity (PWV) value, also DAS 28-CRP and DAS 28-ESR measurement was done in every subject. Others data which also collected in this study are demographic profile, duration and drugs of treatment, random blood glucose, lipid profile, creatinin, and others cardiovascular risk factors. **Results:** 74 subjects met the inclusion criteria, with 68 (91.9%) are women. Mean of AS (PWV) 7,89 (SD 1,92) m/second, which categorized in stiff artery. Mean of DAS 28-CRP 2,46 (SD 0,82) and DAS 28-ESR 3,49 (SD 0,91), each of them was categorized in low and moderate disease activity. In bivariate analysis we found correlation of DAS 28-CRP and DAS 28-ESR to AS (PWV)  $r = 0,529$  ( $p = 0,001$ ) and  $r = 0,493$  ( $p = 0,001$ ). **Conclusion:** There was positive, moderate, and significant correlation between disease activity score (DAS 28-CRP and DAS 28-ESR) with arterial stiffness (PWV).

### ICW-C1-5

#### Predicting future response to biologics by the distribution of affected joints in rheumatoid arthritis patients

Takanori Fujimura, Takashi Fujimoto, Ryota Hara, Naoki Shimmyo, Akira Kido, Yasunori Kobata, Yasuhiro Akai, Yasuhito Tanaka  
The Center for Rheumatic Diseases, Nara Medical University, Kashihara, Japan

Conflict of interest: None

**Objectives:** We analyzed the prognostic significance of data collected at starting biologic agents in patients with rheumatoid arthritis (RA), especially the distribution of affected joints, to predict remission at week 16. **Methods:** Data from 121 RA patients treated with biologic agents at the baseline were used as variables to predict remission. The disease status at the baseline and week 16 was assessed using the disease activity score (DAS28) and patients achieving remission at week 16 were identified according to EULAR criteria ( $DAS28 < 2.6$ ). The mean disease activity at the baseline was 4.95 for DAS28. Sixty-two (51%) and 59 (49%) patients were treated with tumor necrosis factor inhibitors (TNFi) and non-TNFi biologic agents (tocilizumab and abatacept), respectively. All of the patients were classified into 3 groups according to their affected joints which have tenderness or swelling, that is, 1: PIP joints dominant (PIPd) group, 2: MCP joints dominant (MCPd) group, and 3: large joints with wrist joints dominant (L-Wd) group. The correlation of baseline characteristics including the distribution of affected joints with achievement of remission at week 16 was explored by multivariate logistic regression analysis. **Results:** The patients were classified into 16 (13%) of PIPd group, 36 (30%) of MCPd group, and 69 (57%) of L-Wd group. In the patients treated with TNFi, it was disclosed that belonging to PIPd group and lower levels of ESR were independently correlated with achievement of remission ( $p = 0.022$  and  $0.013$ , respectively). In the patients treated with non-TNFi biologic agents, meanwhile, there was no association of the distribution of affected joints with remission and lower levels of DAS28 score was independently correlated with remission. **Conclusion:** We suggested that RA patients predominantly affected with PIP joints were likely to achieve remission in response to TNFi. The distribution of affected joints could predict future response to TNFi in RA patients.

### ICW-C1-6

#### Predictive value of the MBDA score and composite measures for sustained remission at 1 year after withdrawal of adalimumab in the HONOR study

Shintaro Hirata<sup>1</sup>, Kentaro Hanami<sup>1</sup>, Nadine Defranoux<sup>2</sup>, Ippei Miyagawa<sup>1</sup>, Satoshi Kubo<sup>1</sup>, Shunsuke Fukuyo<sup>1</sup>, Norifumi Sawamukai<sup>1</sup>, Kazuhisa Nakano<sup>1</sup>, Shingo Nakayamada<sup>1</sup>, Kazuyoshi Saito<sup>1</sup>, Yoshiya Tanaka<sup>1</sup>

<sup>1</sup>The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Ja-

pan, <sup>2</sup>Crescendo Bioscience Inc., South San Francisco, USA

Conflict of interest: None

[Objectives] We reported predictive value of DAS28ESR at withdrawal of adalimumab (ADA) for subsequent outcomes. Here we investigated the predictive value of the multi-biomarker disease activity (MBDA) score and other composite measures. [Methods] We analyzed 50 patients in the HONOR study (Tanaka Y, et al. Ann Rheum Dis. 2013) observed for 1-year. ADA was withdrawn after maintained in  $DAS28ESR < 2.6$  for at least 24 weeks. Association of DAS28ESR, CDAI, SDAI, and the MBDA score at withdrawal with DAS28ESR or CDAI remission at year 1 was assessed by ROC analysis. MBDA score was derived as 1-100 single integer by Vectra<sup>®</sup> DA algorithm with 12 biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, Leptin, Resistin, CRP, SAA). [Results] Baseline characteristics (mean) were; age 59.5 year, duration 7.1 year, DAS28ESR 5.06, HAQ 0.91. All indices were elevated with time after withdrawal. AUROC and threshold of DAS28ESR, CDAI, SDAI, the MBDA score for DAS28ESR remission ( $< 2.6$ ) was; 0.74, 0.50, 0.49, 0.64, and 1.98, 3.8, 2.0, 26, respectively, and for CDAI remission ( $\leq 2.8$ ) was; 0.64, 0.61, 0.60, 0.63 and 1.61, 0.2, 1.0, 25, respectively. [Conclusion] AUROC was higher in the MBDA score than CDAI or SDAI, and next to DAS28ESR. Threshold in the MBDA score was similar to the remission definition ( $\leq 25$ ), while dissociated in other indices, indicating the MBDA remission as the most relevant target for treatment holiday

### ICW-C2-1

#### Radiographic changes in rheumatoid arthritis patients who treated with the first biological disease-modifying antirheumatic drugs: effect of treatment discontinuation

Kaoru Minegishi<sup>1</sup>, Yukihiko Toyota<sup>1</sup>, Naomi Tsuchida<sup>1</sup>, Yumiko Sugiyama<sup>1</sup>, Yosuke Kunishita<sup>1</sup>, Daiga Kishimoto<sup>1</sup>, Reikou Kamiyama<sup>1</sup>, Maasa Hama<sup>1</sup>, Ryusuke Yoshimi<sup>1</sup>, Yohei Kirino<sup>1</sup>, Mitsuhiro Takeno<sup>2</sup>, Atsuhisa Ueda<sup>1</sup>, Yoshiaki Ishigatsubo<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan, <sup>2</sup>Clinical Laboratory Department, Yokohama City University Hospital, Yokohama, Japan

Conflict of interest: None

[Objectives] To examine the association of radiographic progression and discontinuing the first biological disease-modifying antirheumatic drugs (bDMARD) in patients with rheumatoid arthritis (RA). [Methods] We retrospectively reviewed clinical courses and radiographic changes of RA patients who received bDMARD as the first biologic agent since 2009 in Yokohama City University hospital. The discontinuation rates of bDMARD was evaluated focusing on their first twelve months of treatment. Estimated yearly radiographic progression of the hands was calculated by van der Heijde-modified Sharp score (TSS). [Results] A total of 75 patients (84.0% female, age  $59.7 \pm 14.1$ ) received bDMARD as initial biological therapy (infliximab  $n = 24$ , etanercept  $n = 10$ , adalimumab  $n = 9$ , golimumab  $n = 3$ , tocilizumab  $n = 22$ , abatacept  $n = 7$ ). Nineteen patients (25.3%) discontinued the first bDMARD due to inefficacy ( $n = 9$ ), adverse events ( $n = 9$ ) and other ( $n = 1$ ). There was no significant difference between the baseline characteristics including age, gender, disease duration, DAS28, and ultrasound findings. TSS was unchanged in 54 (72.0%), increased in 18 (24.0%) and decreased in 3 (4.0%) of the patients. Radiographic progression was much greater in patients discontinuing bDMARD than in patients continuing bDMARD (mean change of TSS 1.3 in discontinued group versus 0.5 in continued group,  $p = 0.021$ ). [Conclusion] The prediction of clinical response to initial bDMARD was difficult. However, continuation of bDMARD during the observation period was significantly better in retardation of radiographic progression compared with discontinuation.

### ICW-C2-2

#### Is on-demand ultrasonography assessment in the most affected joint efficient for monitoring RA in daily practice?

Ryusuke Yoshimi<sup>1</sup>, Yukihiko Toyota<sup>1</sup>, Naomi Tsuchida<sup>1</sup>, Yumiko Sugiyama<sup>1</sup>, Yosuke Kunishita<sup>1</sup>, Daiga Kishimoto<sup>1</sup>, Reikou Kamiyama<sup>1</sup>,

Kaoru Minegishi<sup>1</sup>, Maasa Hama<sup>1</sup>, Yohei Kirino<sup>1</sup>, Mitsuhiro Takeno<sup>2</sup>, Atsuhisa Ueda<sup>1</sup>, Yoshiaki Ishigatsubo<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan, <sup>2</sup>Clinical Laboratory Department, Yokohama City University Hospital, Yokohama, Japan

Conflict of interest: None

[Objectives] Although many sets of power Doppler ultrasonography (PDUS) assessment procedures in arbitrary combinations of selected joints have been proposed in monitoring rheumatoid arthritis (RA), they do not always cover all of the affected joints. The aim of the study was to clarify whether US assessment in a selected joint on demand from patients is useful for monitoring RA in daily practice. [Methods] PDUS was performed in 8 joints, including bilateral MCP 2, 3, wrist and knee joints, as a routine in a cumulative total of 207 RA patients. PD signals were scored semiquantitatively from 0 to 3 in each joint, and total PD score-8 was calculated by summing up scores of the 8 joints. Patients declared the most symptomatically affected joint at the examination, and the joint was additionally scanned if it was not included in the routine 8 joints. [Results] One-hundred ten patients had the most affected joint among the routine 8 joints (Group A), whereas 69 had the most affected joint other than the routine joints (Group B). The remaining 28 patients were asymptomatic. PD scores of the most affected joints showed high correlation with total PD score-8 ( $r = 0.52$ ,  $P = 5.8 \times 10^{-14}$ ). For detection of active synovitis of any of the routine joints, the sensitivity and specificity of assessment in the most affected joint were 66.2% and 94.6%, respectively, in the symptomatic groups, 82.6% and 100% in Group A, and 36.0% and 89.5% in Group B. In two patients (2.9%) of Group B, PD signals were detected in the most affected joints despite the total PD score-8 was 0. These data indicated that US finding in the most affected joint represents those of the routine 8 joint examination in Group A, whereas it gives supplemental information to the routine examination in Group B. [Conclusion] This study suggests that, in combination with total PD score-8, on-demand US assessment in the most affected joint is efficient for management of RA patients in daily practice.

### ICW-C2-3

#### Concordance between joint symptom/swelling/tenderness and US synovitis: Which clinical finding is more relevant to US?

Ayako Hirata, Takehisa Ogura, Norihide Hayashi, Sayaka Takenaka, Hideki Ito, Kennosuke Mizushima, Sumie Nakahashi, Yuki Fujisawa, Hideto Kameda

Division of Rheumatology, Toho University Ohashi Medical Center, Tokyo, Japan

Conflict of interest: None

[Objectives] Recently ultrasonography (US) has been prevalent as a valid and objective modality of joint examination in patients with rheumatoid arthritis (RA). However, few studies have reported the agreement between subjective joint symptoms and US synovitis at each joint level. Therefore, we examined and compared the concordance between joint symptom/swelling/tenderness and US synovitis. [Methods] 44 patients with RA (86% female, the mean age of 68 years) were asked for the self-evaluation of joint symptoms including pain and considerable stiffness in (proximal) interphalangeal, metacarpophalangeal, wrist, elbow, shoulder, knee and ankle joints. Those joints were evaluated by physical examination for the presence of tenderness and/or swelling, and also by US for the presence of synovitis defined as gray-scale score  $\geq 2$  or power Doppler signal score  $\geq 1$ . [Results] The overall concordance rate with US synovitis was poor for joint tenderness ( $\kappa=0.30$ ) when compared with joint symptoms ( $\kappa=0.40$ ) or swelling ( $\kappa=0.44$ ). Moreover, the percentage of inflamed joint clinically detected only by joint symptom, swelling, and tenderness was 3.6%, 1.8% and 0.5%, respectively, when US synovitis was defined as a gold standard. [Conclusion] Although patient-reported joint symptoms are clinically important, joint examination for the presence of tenderness can be, instead, excluded from clinical joint assessment. A recent proposal of the modification of composite activity measures such as disease activity score (DAS) 28 and simplified disease activity index (SDAI) by removing tender joint count (and patient's global assessment) may support our results.

### ICW-C2-4

#### Examination of ultrasound (US) findings of elderly onset rheumatoid arthritis (RA) who had polymyalgia rheumatica (PMR)-like symptoms

Norihide Hayashi, Takehisa Ogura, Ayako Hirata, Rie Kujime, Hideki Ito, Munetsugu Imamura, Sayaka Takenaka, Kennosuke Mizushima, Sumie Nakahashi, Naoko Yamashita, Yuki Fujisawa, Hideto Kameda  
Toho University Medical Center Ohashi Hospital, Tokyo, Japan

Conflict of interest: None

[Objectives] Elderly (>65 years) onset RA (EORA) has a characteristics of acute onset and high activity without typical clinical symptoms and serological findings. Therefore, the differential diagnosis from other rheumatic diseases such as PMR and crystal-induced arthritis is critical. We elucidated the clinical importance of the joint US examination in the diagnosis of seronegative EORA. [Methods] 11 patients (5 male, the mean age of 76.5) diagnosed with seronegative EORA presenting with PMR-like symptoms were examined. [Results] Edema of peripheral limbs were clinically observed in 73% of patients, and tenosynovitis was detected in all patients in addition to the joint synovitis or bone erosions by US. Tenosynovitis were observed frequently in wrist (82%) and shoulder (63%), the former suggesting the association with peripheral edema. Although glucocorticoids had been included in the initial treatment in 82% of patients, it was discontinued (27.3%) or reduced to less than 5mg/day (63.6%) within six months. [Conclusion] US is useful for EORA diagnosis by detecting small bone erosion and/or synovitis even in patients with edema.

### ICW-C2-5

#### Survey of Current Trends in Clinical Use of Ultrasound for Rheumatoid Arthritis in Japan: Focusing on Power Doppler Setting for Future Standardization and Machine-to-Machine Calibration

Tamotsu Kamishima<sup>1</sup>, Akihiro Narita<sup>2</sup>, Kazuhide Tanimura<sup>2</sup>, Takao Koike<sup>3</sup>

<sup>1</sup>Faculty of Health Science, Hokkaido University, Sapporo, Japan, <sup>2</sup>Hokkaido Medical Center for Rheumatic Diseases, Sapporo, Japan, <sup>3</sup>Sapporo Medical Center NTT EC, Sapporo, Japan

Conflict of interest: None

[Objectives] Despite the advantages of ultrasound (US) in the management of rheumatoid patients, the lack of standardization of machine setting prevents the production of strong evidence for the clinical application of US. We conducted a study to survey the current trends in diversity of US machine models and their settings used for rheumatoid patients in Japan. [Methods] A questionnaire was mailed to the members of one of the major domestic study groups for US in rheumatology. Responses were entered in an electronic database. Results were analyzed quantitatively or summarized qualitatively in the case of open questions. [Results] The overall response rate was 61.7%(37/60). Twenty different models of US machine and 26 models of probe were used, resulting in 34 patterns of combination. The most frequently used combination was found in eight facilities. The pulse repetition frequency setting was not constant after being changed from the "preset" for more than 70% of the machines. [Conclusion] Ultrasonographical equipment and its settings are varied in each facility in Japan, making it difficult to conduct a multi-center trial in the current situation. Standardization and calibration is the next step for enhanced use of US in rheumatology practice.

### ICW-C2-6

#### Usefulness of whole-body MRI for the evaluation of patients with rheumatoid arthritis on biological agents

Michihito Kono<sup>1,2</sup>, Shinsuke Yasuda<sup>1</sup>, Kazumasa Ohmura<sup>1</sup>, Sanee Shimamura<sup>1</sup>, Atsushi Noguchi<sup>1</sup>, Ikuma Nakagawa<sup>1</sup>, Haruki Shida<sup>1</sup>, Toshiyuki Watanabe<sup>1</sup>, Yuka Shimizu<sup>1</sup>, Kenji Oku<sup>1</sup>, Toshiyuki Bohgaki<sup>1</sup>, Olga Amengual<sup>1</sup>, Tetsuya Horita<sup>1</sup>, Tamotsu Kamishima<sup>3</sup>, Tatsuya Atsumi<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, Sapporo, Japan, <sup>2</sup>Hokkaido P.W.F.A.C Obihiro-Kosei General Hospital, Obihiro, Japan, <sup>3</sup>Faculty of Health Science, Hokkaido University, Sapporo, Japan



Conflict of interest: None

[Objectives] To evaluate the usefulness of whole-body MRI (WBMRI) for patients with rheumatoid arthritis (RA) on biological agents (Bio). [Methods] A total of 30 consecutive RA patients on Bio between 2006 and 2014 were included in this retrospective study. Contrast WBMRI was performed before and one year after the initiation of Bio. Hand joints were evaluated according to RA MRI score (RAMRIS) and the other joints (atlantoaxial, shoulder, hip, and knee joints) were scored in the modified RAMRIS. [Results] Mean age was 57.1 years old and mean duration of the disease 3.0 years. Mean DAS28-ESR improved from 5.3 to 2.5 ( $p < 0.01$ ). Bio treatment led to improvement in whole-body synovitis score ( $p = 0.02$ ) from  $31.2 \pm 14.6$  to  $23.2 \pm 11.3$ , as well as in whole-body bone edema score ( $p = 0.03$ ) from median [range]; 11 [1-54] to 3 [0-43]. WBMRI-bone-erosion-score improved in seven patients and deteriorated in 17 patients. Logistic regression analysis showed whole-body synovitis score ( $p = 0.04$ ) was identified as a poor prognostic factor for the progression of WBMRI-bone-erosion. Changes in RAMRIS bone edema or erosion score of hands did not correlate with those in modified RAMRIS score of other joints in WBMRI. [Conclusion] WBMRI is useful for the evaluation of patients with RA.

### ICW-C2-7

#### The assessment between tenderness pain of the shoulder joint and the inflammations on shoulder magnetic resonance imaging in patients with rheumatoid arthritis

Satoshi Shinagawa, Koichi Okamura, Yukio Yonemoto, Chisa Okura, Takahito Suto, Tsuyoshi Sasaki, Tsuyoshi Tajika, Kenji Takagishi  
Orthopaedic Surgery, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

Conflict of interest: None

[Objectives] To evaluate the association between shoulder tenderness pain and the inflammations on shoulder magnetic resonance imaging (MRI) in patients with rheumatoid arthritis (RA). [Methods] Forty-two shoulders 41 patients who met the American College of Rheumatology (ACR) revised criteria in 1987 were examined with MRI. They included 24 shoulders with tenderness of the shoulder joint and 18 shoulders without it. We counted the number of sites detected as positive for synovitis among 5 sites; Axillary pouch, Sub-acromial bursa, Sub-deltoid bursa, Rotator interval and Biceps pulley, erosion among 5 sites; Supraspinatus insertion site, Infraspinatus insertion site, Subscapularis insertion site, Joint surface of the humeral head and Glenoid fossa and bone marrow edema among 4 sites; Supraspinatus insertion site, Infraspinatus insertion site, Subscapularis insertion site and Subchondral area of the humeral head in the shoulder joint, and also assessed the presence or absence of rotator cuff tear on MRI of patients. The difference of their background factors and MRI findings between the groups with or without shoulder tenderness was evaluated. In addition, logistic analysis was performed to elucidate the factor with shoulder tenderness. [Results] The numbers of positive sites for MRI findings in the groups with/without shoulder tenderness were as follows; synovitis:  $3.0 \pm 1.4 / 0.7 \pm 1.0$ , erosion:  $3.0 \pm 1.6 / 2.3 \pm 1.3$  and bone marrow edema:  $2.2 \pm 1.3 / 1.2 \pm 1.4$  (mean  $\pm$  SD). There was a significant differences in synovitis and bone marrow edema ( $p < 0.001$  and  $p = 0.027$ ) between with or without shoulder tenderness. After logistic regression analysis, the most strongly associated factor with shoulder tenderness was the synovitis on MRI (OR 3.8). [Conclusion] The inflammations on MRI were represented with the number of positive sites in rheumatoid shoulder. Our study indicated that the most strongly association between shoulder tenderness and synovitis on MRI in patients with RA.

### ICW-C3-1

#### Long-term clinical efficacy and safety of abatacept: results from consecutive 508 patients with rheumatoid arthritis in a Japanese multicenter registry

Nobunori Takahashi, Toshihisa Kojima, Koji Funahashi, Naoki Ishiguro  
Nagoya University Graduate School of Medicine, Nagoya, Japan

Conflict of interest: None

[Objectives] Abatacept (ABT) is a new biologic drug and has been available for rheumatoid arthritis (RA) patients since 2010 in Japan. There has been little evidence showing long-term results of ABT. The aim of this study is to demonstrate four-year clinical results including drug adherence and potential factors affecting drug discontinuation. [Methods] Participants were consecutive 508 patients with RA who were prospectively registered in the Tsurumai Biologics Communication Registry and treated with ABT. Survival analysis was performed with the Kaplan-Meier method and log-rank test. [Results] At baseline, mean age was 65.1 years, disease duration was 13.1 years, and DAS28-CRP was 4.36. Of the 508 patients, 78.8% was female, 77.5% was RF positive ( $>20$  mg/dl), and 42.7% had prior biologics history (Bio-switch). Overall drug retention rate was 78.8% at 1 year and 56.8% at 4 years. Discontinuation rate due to adverse events was 4.3% at 1 year and 8.2% at 4 years. Bio-switch patients demonstrated significantly higher discontinuation rate due to inadequate efficacy compared to Bio-naïve patients (32.3 vs 8.9%,  $p < 0.001$ ). Among the Bio-switch patients, RF negative patients demonstrated significantly higher discontinuation rate due to secondary failure compared to RF positive patients (40.8 vs 11.0%,  $p = 0.025$ ). The hazard ratio for secondary failure, adjusted for sex, age, disease duration, concomitant MTX and PSL, and baseline DAS28-CRP, was 4.17 (95%CI 1.20-14.45) for RF negative versus RF positive. On the other hand, RF positivity did not affect the discontinuation rate in the Bio-naïve patients. [Conclusion] ABT demonstrated satisfactory four-year retention rate and safety profile. We found that RF negative Bio-switch patients had quite high discontinuation rate due to secondary failure. It is necessary to establish the strategy for additional therapeutic intervention, such as concomitant drugs, in this patients group to improve the long-term clinical results of ABT.

### ICW-C3-2

#### Multicenter prospective trial for rheumatoid arthritis using Abatacept in Japanese patients, an investigator-initiated study (Mt. Fuji Study)

Noriyoshi Ogawa<sup>1</sup>, Toshiaki Miyamoto<sup>2</sup>, Hiroyuki Ohashi<sup>3</sup>, Yasuhiro Ota<sup>4</sup>, Kaori Kobori<sup>5</sup>, Motohiro Suzuki<sup>6</sup>, Seiji Tsuboi<sup>7</sup>, Masakatsu Hayakawa<sup>8</sup>, Yoshinori Goto<sup>9</sup>, Taro Karahashi<sup>10</sup>, Osamu Kimoto<sup>11</sup>, Kumiko Shimoyama<sup>1</sup>, Daisuke Suzuki<sup>1,12</sup>

<sup>1</sup>Internal Medicine 3, Division of Immunology and Rheumatology, Hamamatsu University School of Medicine, Hamamatsu, Japan, <sup>2</sup>Seirei Hamamatsu General Hospital, Japan, <sup>3</sup>Omaezaki Municipal Hospital, Japan, <sup>4</sup>Yasuhiro Clinic, Japan, <sup>5</sup>Kobori Orthopaedic Clinic, Japan, <sup>6</sup>Department of Orthopedic Surgery, Hamamatsu University School of Medicine, Japan, <sup>7</sup>Shizuoka Kosei Hospital, Japan, <sup>8</sup>Hayakawa Clinic, Japan, <sup>9</sup>Goto Clinic, Japan, <sup>10</sup>Fujieda Municipal Hospital, Japan, <sup>11</sup>Kimoto Clinic, Japan, <sup>12</sup>Iwata City Hospital, Japan

Conflict of interest: None

[Objectives] To assess the efficacy and safety of abatacept in Japanese patients with rheumatoid arthritis (RA). [Methods] In this two-year multicenter prospective study, RA patients who had an inadequate or unsustained response to at least one disease-modifying anti-rheumatic drug were subjected. Disease activity score in 28 joints (DAS28 (CRP)) and joint damage progression (modified-total Sharp score (mTSS)) were evaluated. Safety was assessed throughout the study. [Results] 109 RA patients participated in this study from October 2010 to September 2012. The mean age was 61.7 year-old (range 32~84), male: female = 20: 89, mean disease duration was 9.2 years (3m~45y). 27 were on methotrexate (MTX), 81 were not. Mean MTX dosage was 9.1 mg/week. 48 were Bio-Naïve, and 61 were Bio-Switched. At two-year, discontinuations due to 15 insufficient efficacy, 9 adverse events, and 3 remission were noted. There were no serious adverse events. At baseline, Bio-Naïve patients had a mean DAS28 (CRP) of  $4.5 \pm 1.1$ , Bio-Switched patients had a mean DAS28 (CRP) of  $4.9 \pm 1.2$ . The DAS28 (CRP) decreased to  $2.5 \pm 1.3$  in Bio-Naïve and to  $3.3 \pm 1.5$  in Bio-Switched at two-year. At two-year, significantly greater proportion of Bio-Naïve patients achieved remission compared to Bio-Switched patients (54.5% vs 28.2%;  $p < 0.01$ ). There was significantly less radiographic progression at two-year compared to baseline (mean yearly progression in mTSS, baseline vs two-year: 4.69 vs 0.07 in Bio-Naïve;  $p < 0.01$ , 6.38 vs 0.26 in Bio-Switched;  $p < 0.01$ ). [Conclusion] These findings suggest that abatacept is useful and more effective in Bio-naïve compared to Bio-switched in Japanese RA patients, and that abatacept has an ability to suppress radiographic progression.

### ICW-C3-3

#### Concomitant methotrexate scarcely augment the clinical efficacy of abatacept in patients with rheumatoid arthritis: a propensity score matching analysis

Nobunori Takahashi, Toshihisa Kojima, Koji Funahashi, Naoki Ishiguro  
Nagoya University Graduate School of Medicine, Nagoya, Japan

Conflict of interest: None

[Objectives] Abatacept (ABT), a selective T-cell co-stimulation modulator, is a new biologic drug and has been available for rheumatoid arthritis (RA) patients since 2010 in Japan. We have previously reported that concomitant methotrexate (MTX) therapy did not significantly affect the clinical efficacy of ABT. The aim of this study is to confirm our initial finding by using propensity score matching analysis. [Methods] Participants were consecutive 419 patients with RA who were prospectively registered in the Tsurumi Biologics Communication Registry, treated with ABT, and followed up for at least 52 weeks. One-to-one matched pairs between the patients with and those without concomitant MTX treatment were generated by using the propensity score with a matching model. Survival analysis was performed with the Kaplan-Meier method and the log-rank test. [Results] Unadjusted analysis consisted of 217 and 202 patients treated with and without concomitant MTX treatment, respectively. The propensity score adjusted analysis consisted of 52 patients each. Unadjusted analysis demonstrated that the mean DAS28-CRP score at 52 weeks in the patients with MTX was significantly lower than that in the patients without MTX (2.83 vs 3.27,  $p < 0.01$ ), while there was no difference at baseline. The adjusted analysis demonstrated there was no significant difference in the mean DAS28-CRP score between the groups at baseline (4.68 vs 4.51,  $p = 0.490$ ) and also at 52 weeks (3.11 vs 3.22,  $p = 0.668$ ). The patients with and those without MTX usage demonstrated equivalent drug retention rate at 52 weeks (79.4 vs 83.6%,  $p = 0.678$ ). [Conclusion] Unadjusted analysis using greater number of patients compared to our previous study apparently showed the superiority of concomitant MTX usage for clinical efficacy of ABT. However, the analysis with careful adjustment using propensity score matching clearly revealed that the increasing effect of concomitant MTX on ABT efficacy was practically limited.

### ICW-C3-4

#### Efficacy and tolerance of abatacept in patients with rheumatoid arthritis for 3 years

Yuji Kukida<sup>1</sup>, Aiko Tominaga<sup>1</sup>, Risa Sagawa<sup>1</sup>, Takashi Kida<sup>1</sup>, Amane Nakabayashi<sup>1</sup>, Kazuki Fujioka<sup>1</sup>, Hidetake Nagahara<sup>1</sup>, Wataru Fujii<sup>1</sup>, Ken Murakami<sup>1</sup>, Takahiro Seno<sup>1,2</sup>, Aihiro Yamamoto<sup>1</sup>, Masataka Kohno<sup>1</sup>, Yutaka Kawahito<sup>1</sup>

<sup>1</sup>Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>2</sup>Department of Rheumatic Diseases and Joint Function, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: Yes

[Objectives] To evaluate efficacy and tolerance of abatacept (ABT) for 3 years in patients with rheumatoid arthritis (RA). [Methods] Twenty five RA patients treated with ABT for 3 years in our department are included in this study. Mean age was 56.6 years old, mean disease duration was 7.8 years, and 18 patients were treated with methotrexate (MTX). Seven patients had no history of biological agents use. Efficacy was evaluated based on DAS28-CRP, SDAI, and Boolean remission criteria. [Results] Mean DAS28-CRP was 3.97/2.76/2.63/2.62 (baseline/1year/2years/3years), and mean SDAI was 27.1/14.0/12.9/13.1 respectively. The efficacy of ABT emerged by 6 months, and the efficacy was sustained until 3 years. Contributing factors for effectiveness were no previous biologics use and short disease duration. Remission rate at 3 years was 24/28% (SDAI/Boolean criteria). Drug survival rate was 64%. Infections were the most common adverse events. There was no case that ABT was discontinued due to adverse events. [Conclusion] This study indicated that ABT can provide sustained efficacy and consistent safety for 3 years. The predictors for good response were no previous biologics use and short disease duration.

### ICW-C3-5

#### Discontinuation of tofacitinib after achieving low-disease activity (LDA) in patients with established rheumatoid arthritis (RA)

Satoshi Kubo<sup>1</sup>, Kazuhisa Nakano<sup>1</sup>, Shingo Nakayamada<sup>1</sup>, Shintaro Hirata<sup>1</sup>, Shunsuke Fukuyo<sup>1</sup>, Ippei Miyagawa<sup>1</sup>, Akio Kawabe<sup>1</sup>, Kazuyoshi Saito<sup>1</sup>, Kunihiro Yamaoka<sup>2</sup>, Yoshiya Tanaka<sup>1</sup>

<sup>1</sup>The 1st Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] The possibility of biologics-free disease control was demonstrated in patients with RA. However, evidences of targeted sDMARDs-free disease control after discontinuing tofacitinib in RA patients in clinical practice have not been investigated. The aim of this study is to investigate the possibility of discontinuing tofacitinib, a JAK inhibitor, for 6 months without flaring and to identify factors to keep tofacitinib-free. [Methods] Of 47 patients treated with tofacitinib, 24 patients achieved LDA without adverse events in the clinical trial. 21 patients went on discontinuation of tofacitinib with their consent. The primary endpoint was the tofacitinib-free rate (without escalation of MTX or tofacitinib re-administration) at 6 month by using LOCF method. [Results] The age of 21 patients was 60.3 years old with the mean disease duration of 5.2 years, 81% concomitant MTX (8.9 mg/w), SDAI 2.8, RF 44.8 U/ml, ACPA 82.6 U/ml, and MMP-3 46.7 ng/ml at the time of discontinuation. Out of 21 patients, 14 (67%) were maintained discontinuation of tofacitinib for 6 months. 81% and 43%(100% and 67% at baseline) of patients achieved LDA and remission at 6 month, respectively. Univariate analysis revealed that there were significant differences of the disease duration (4.4 vs 9.1 years) and the titer of ACPA (43.1 vs 161.6 U/ml) between the patients who achieved discontinuation and the patients who did not. Dividing into 2 groups by the titer of ACPA, 90% of patients achieved LDA in low ACPA group at 6 month, while 70% of patients achieved in high ACPA group. On the other hand, in the patients who could not achieve discontinuation, escalation of MTX in 5 patients and re-initiating tofacitinib in 2 patients resulted in the reduction of disease activity. [Conclusion] It was possible to discontinue tofacitinib without flaring in patients with established RA.

### ICW-C3-6

#### The combination therapy of iguratimod with methotrexate

Koichi Okamura<sup>1,2</sup>, Yukio Yonemoto<sup>1</sup>, Takahito Suto<sup>1</sup>, Chisa Okura<sup>1</sup>, Kenji Takagishi<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine, Gunma, Japan, <sup>2</sup>Department of Orthopaedics, Alpert Medical School of Brown University and Rhode Island Hospital, Providence, Rhode Island, USA

Conflict of interest: None

Objective: In recent years, the usefulness of synthetic chemical compounds that act as disease-modifying antirheumatic drugs (DMARDs) has been reported for the treatment of rheumatoid arthritis (RA). We performed a 52-week study on the efficacy and safety of the combination of iguratimod (IGU) with methotrexate (MTX) against patients with RA in daily clinical use. Methods: Twenty-four patients (7 male, 17 female, mean age of 65.7±12.0, mean disease duration of 16.8±12.6), who met the 1987 American College of Rheumatology criteria for the classification of RA from September 2012 to April 2013, were enrolled in this study. The clinical course of RA was regularly evaluated during the 52 weeks of treatment. The last observation carried forward (LOCF) method was applied to assess the patients who discontinued the IGU therapy. Results: The survival rate of IGU with MTX at week 52 was 75.0%. The disease activity score (DAS) 28 - erythrocyte sedimentation rate, DAS28 - C-reactive protein (CRP), simplified disease activity index (SDAI), clinical disease activity index (CDAI) and the matrix metalloproteinase (MMP)-3 level were all significantly decreased at week 52. There were one case of the onset of interstitial pneumonia (IP) and one case of the onset of Pneumocystis jirovecii pneumonia. Conclusions: The combination of IGU with MTX is a long-term and efficient way of controlling the disease activity of RA.

### ICW-C4-1

#### Association of serum low-density lipoprotein cholesterol levels with disease activity and genetic factors in Japanese patients with rheumatoid arthritis: results from the IORRA cohort study

Shinji Yoshida<sup>1,2</sup>, Katsunori Ikari<sup>1</sup>, Atsuo Taniguchi<sup>1</sup>, Hisashi Yamanaka<sup>1</sup>, Shigeki Momohara<sup>1</sup>

<sup>1</sup>Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Keio University School of Medicine

Conflict of interest: None

[Objectives] Genetic determinants of serum low-density lipoprotein cholesterol (LDL-C) levels are well characterized in the general population. To date, LDL-C has been reported to be associated with disease severity in rheumatoid arthritis (RA). However, data on lipid profiles in patients with RA have been different depending on reports. The purpose of our study was to evaluate the influence of clinical and therapeutic data including disease activity and glucocorticoid use on LDL-C, and to identify genetic variants associated with serum LDL-C levels in Japanese patients with RA. [Methods] This study included 6,920 Japanese patients with RA from the Institute of Rheumatology Rheumatoid Arthritis cohort study (IORRA). The DNA samples were obtained from 1,263 patients. *HLA-DRB1* shared epitope (SE) and 21 single nucleotide polymorphisms (SNPs) in susceptibility genes to RA and 13 SNPs modulating serum LDL-C levels validated in the Japanese general population were genotyped. First, association of serum LDL-C levels was examined with clinical and therapeutic data by a multivariate linear regression analysis adjusted for lipid-lowering drug use in 6,920 patients. Secondly, genetic association of LDL-C was investigated with *HLA-DRB1* SE and each SNP by multivariate linear regression analyses in 1,263 patients. Adjustments were made for non-genetic factors with significant association in the primary analysis. [Results] The primary analysis showed that older age, female gender, high BMI, lower DAS28 and glucocorticoid use were significantly associated with higher serum LDL-C levels. The secondary analyses revealed that patients with more minor alleles of rs7412 in *APOE* had higher serum LDL-C levels ( $P = 3.1 \times 10^{-9}$ ), but no susceptibility genes to RA had such association. [Conclusion] Our results indicate that suppressing inflammation contributes to elevate serum LDL-C levels and an *APOE* polymorphism is a genetic risk factor for higher serum LDL-C levels in Japanese patients with RA.

### ICW-C4-2

#### Association between lack of response in disease activity and acute exacerbation of interstitial lung disease during tocilizumab treatment in patients with rheumatoid arthritis

Mitsuhiro Akiyama, Yuko Kaneko, Tsutomu Takeuchi

Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] To investigate risk factors associated with acute exacerbation (AE) in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) during tocilizumab (TCZ) treatment. [Methods] All consecutive 390 RA patients treated with TCZ at our institution from June 2008 to September 2014 were retrospectively reviewed. We classified them into RA-ILD group or non-ILD group according to high-resolution CT (HRCT) findings. RA-ILD group was further divided into AE group or non-AE group according to the occurrence of AE. We compared the groups regarding the baseline variables and the response to TCZ. [Results] A total of 75 patients (19.2 %) were included in RA-ILD group. Multivariate analysis revealed that male (RR 3.64; 95% CI 1.67 to 7.94;  $p=0.001$ ), age over 60 (RR 9.60; 95% CI 3.34 to 27.62;  $p<0.0001$ ), and the positivity of rheumatoid factor (RF) (RR 16.14; 95% CI 2.10 to 123.97;  $p=0.008$ ) were associated with RA-ILD. Of 75 patients in RA-ILD group, a total of 6 patients (8%) developed AE during TCZ therapy, with an incidence of 3.39 per 100 person-year. The median duration between the commencement of TCZ and the AE occurrence was 12 (range 8 to 30) months. None of patients in AE group was treated with concomitant methotrexate. Whereas mean DAS28 at baseline was not statistically different between non-AE group and AE group (4.67 vs 4.17,  $P=0.484$ ), mean DAS28 at 12 weeks after initiating TCZ therapy was significantly

better in non-AE group than in AE group (2.3 vs 4.6,  $P<0.0001$ ), and more patients in non-AE group achieved remission or low disease activity than in AE group (89.7% vs 0%,  $P<0.0001$ ). The other background characteristics, including age, sex, disease duration, history of smoking, the positivity of anticyclic citrullinated peptide antibodies (anti-CCP) and RF, KL-6 and HRCT pattern were also not statistically different. [Conclusion] Poor response at 12 weeks but not baseline DAS28 may be associated with AE in RA-ILD.

### ICW-C4-3

#### Serum GM-CSF levels are significantly associated with interstitial pneumonia (IP) in biologic-naive patients with rheumatoid arthritis (RA): a single-center prospective cohort study (Keio First-Bio Cohort Study)

Keisuke Izumi<sup>1</sup>, Misato Hashizume<sup>2</sup>, Keiko Yoshimoto<sup>1</sup>, Yuko Kaneko<sup>1</sup>, Hidekata Yasuoka<sup>1</sup>, Katsuya Suzuki<sup>1</sup>, Kunihiro Yamaoka<sup>1</sup>, Tsutomu Takeuchi<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, <sup>2</sup>Product Research Department, Fuji-Gotemba Research Laboratories, Chugai Pharmaceutical Co., Ltd., Gotemba, Japan

Conflict of interest: None

**Objectives:** IP is one of the most critical complications in RA. We aimed to explore the associations between IP and serum cytokines in biologic-naive patients with RA. **Methods:** Consecutive biologic-naive patients with RA were enrolled in our prospective cohort study at the timing of initiating biologics. Our cohort started in February 2010, and the patients were analysed as of April 2012. Before initiating biologics, we evaluated chest X-rays for all of the patients, and if IP was suspected, a chest computed tomographic (CT) scan was taken. We assessed variables at the enrollment of our cohort including the patients' characteristics (age, disease duration, prednisolone (PSL) dose, MTX dose, CDAI, HAQ, mTSS) and serum biomarker levels (IgG, IgM, IgM-RF, ACPA, CRP, MMP-3, GM-CSF, IFN- $\gamma$ , IL-1 $\beta$ , IL-2, IL-6, IL-8, IL-10, IL-12p70, IL-17, TNF- $\alpha$ , VEGF, sICAM-1, BAP, osteonectin, osteopontin) to extract factors associated with CT scan-proven IP using univariate analyses. The extracted variables ( $P<0.1$ ) were applied to a stepwise selection method, and the selected variables were entered into a multivariate logistic regression model to obtain factors associated with IP. **Results:** A total of 127 patients (108 females and 19 males) were included in our study. The mean age and disease duration of the patients were  $56.2 \pm 12.9$  years and  $6.7 \pm 7.7$  years, respectively. CT scan-proven IP was noted in 17 patients. PSL was used in 33 patients and MTX was used in 110. In the univariate analyses, age, PSL dose, MTX dose, GM-CSF, IL-1 $\beta$ , and VEGF were significantly associated ( $P<0.05$ ), and IL-8 and TNF- $\alpha$  tended to be associated with IP ( $P<0.1$ ). In the multivariate analyses, age (OR 1.093, 95% CI 1.033-1.173), MTX dose (0.829, 0.705-0.969), and the levels of GM-CSF (1.376, 1.081-2.042) were identified as factors associated with IP. **Conclusion:** The high serum levels of GM-CSF as well as high age and low MTX dose are significantly associated with IP in biologic-naive patients with RA.

### ICW-C4-4

#### Increased Left Ventricular Mass Index and Decreased Ejection Fraction Are Associated with Disease Activity in Rheumatoid Arthritis Patients; assessed by Cardiac Magnetic Resonance Imaging

Hitomi Haraoka<sup>1</sup>, Isamu Yokoe<sup>2</sup>, Atsuma Nishiwaki<sup>1</sup>, Kaita Sugiyama<sup>1</sup>, Yosuke Nagasawa<sup>1</sup>, Natsumi Ikumi<sup>1</sup>, Takamasa Nozaki<sup>1</sup>, Hirotake Inomata<sup>1</sup>, Hidetaka Shiraiwa<sup>1</sup>, Noboru Kitamura<sup>1</sup>, Masami Takei<sup>1</sup>

<sup>1</sup>Division of Hematology and Rheumatology, Nihon University School of Medicine, Tokyo, Japan, <sup>2</sup>Itabashi Chuo Medical Center, Japan

Conflict of interest: None

[Objectives] Patients with rheumatoid arthritis (RA) experience an excess risk of congestive heart failure (CHF). Cardiac magnetic resonance imaging (CMR) has been used to identify early functional and structural changes in the left ventricle (LV) before development of clinically overt CHF. We evaluated LV function and structure using a CMR in RA patients (pts) without cardiac symptoms, and determined the impact

of cs (conventional synthetic) and biologic DMARDs (bDMARDs). [Methods] Consecutive RA pts and healthy control without a history or clinical findings of hypertension, cardiovascular disease, diabetes, or dyslipidemia were enrolled. RA pts received biologic or csDMARDs. All subjects underwent evaluation of LV function and structure using non-contrast CMR. LV function was based on LV ejection fraction (EF). LV hypertrophy was measured by absolute LV mass (LVM) and LV mass index (LVMI) determined by LVM/body surface area. [Results] We compared 90 female RA pts (mean age, 55.9±7.1 years) with a matched 20-patient control group (mean age, 52.7±4.6 years). 46 RA pts received csDMARDs and 44 RA pts received bDMARDs plus MTX (8.0±1.4 mg). SDAI score was significantly higher in the csDMARDs group than in the bDMARDs group ( $p=0.002$ ). Compared to the control group, the bDMARDs group showed significantly higher LVMI and lower EF ( $p<0.001$ ,  $p=0.003$ , respectively). There were no significant differences in LVMI and EF between the control and the bDMARDs groups. Among those with abnormal LV geometry, 32% of RA patients in the csDMARDs group showed eccentric hypertrophy. 98% of RA patients in the bDMARDs group showed normal geometry. LVMI and EF were significantly associated with SDAI ( $p<0.001$ ,  $p=0.02$ , respectively). Adjustment for ESR did not modify the association of SDAI with EF and LVMI ( $p=0.017$ ,  $p=0.005$ , respectively). [Conclusion] Our findings can be presumed that disease activity may be an important contributor to the development of LV abnormalities in RA.

#### ICW-C4-5

##### A retrospective study of the risk of hyperlipidemia and ischemic heart disease in patients with rheumatoid arthritis in Taiwan

Ning-Sheng Lai<sup>1</sup>, Malcolm Koo<sup>2</sup>

<sup>1</sup>Clinical Center of Rheumatology and Immunology, Dalin Tzu Chi General Hospital, Dalin, Taiwan, <sup>2</sup>School of Medicine, Tzu Chi University, Hwa-Lan, Taiwan

Conflict of interest: None

**Objectives:** To evaluate the prevalence of hyperlipidemia and ischemic heart disease among Taiwanese patients with rheumatoid arthritis (RA), a retrospective study aimed to investigate the risk of hyperlipidemia and ischemic heart disease were performed. **Methods:** A retrospective study was performed using the computerized patients' record database in a regional hospital in south Taiwan. A total of 2,869 patients with a diagnosis of RA (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 714.0) since the inauguration of the study hospital in July 2000 until July 2014 were included. The RA cases were matched on age and sex with 11,448 patients without RA. The risks of hyperlipidemia (ICD-9-CM codes 272.0, 272.2, 272.4, and 272.9) and ischemic heart disease (ICD-9-CM codes 410.x-414.x) in patients with RA were evaluated using multivariate logistic regression analyses, adjusting for comorbidities. **Results:** Multivariate logistic regression analysis revealed a significant association between hyperlipidemia and RA (adjusted odds ratio [OR] = 2.03,  $p < 0.001$ ). Similar associations were observed in both male and female patients. In addition, multivariate logistic regression analysis indicated a significant association between ischemic heart disease and hyperlipidemia (OR=3.45,  $P < 0.001$ ) in RA patients. **Conclusion:** Findings from this retrospective study indicated that RA was significantly associated with the risk of hyperlipidemia. Given the strong association between hyperlipidemia and ischemic heart disease, clinicians are advised to be vigilant for the risk of ischemic heart disease among patients with RA.

#### ICW-C4-6

##### Coincidence of achalasia and autoimmune diseases (Four such cases)

Yoshinori Katada<sup>1</sup>, Akihiko Nakabayashi<sup>1</sup>, Yuta Yamaguchi<sup>1</sup>, Sara Murakami<sup>1</sup>, Madoka Morimoto<sup>1</sup>, Yoshinori Harada<sup>2</sup>, Akiko Yura<sup>2</sup>, Maiko Yoshimura<sup>2</sup>, Eriko Tanaka<sup>2</sup>, Satoru Teshigawara<sup>2</sup>, Michihito Katayama<sup>2</sup>, Soichiro Tsuji<sup>2</sup>, Masato Matsushita<sup>2</sup>, Shiro Ohshima<sup>2</sup>, Jun Hashimoto<sup>2</sup>, Yukihiko Saeki<sup>2</sup>, Johji Kohno<sup>3</sup>, Kazushi Konma<sup>3</sup>

<sup>1</sup>Department of Rheumatology, Sakai City Hospital, Sakai City, Japan,

<sup>2</sup>Department of Allergology and Rheumatology, NHO Osaka Minami Medical Center, Kawachinagano, Japan, <sup>3</sup>Sakai City Hospital, Sakai City, Japan

Conflict of interest: None

**[Objectives]** Esophageal achalasia is a rare disease characterized by degeneration of Auerbach's plexus. Although its presumed etiologies include autoimmune process, their significance in autoimmune diseases remain uncertain. **[Methods]** [A] The computerized medical records of Osaka-minami Medical Center were screened for patients with systemic lupus erythematosus (SLE), systemic sclerosis (SSc), myositis, and achalasia for recent 30 years (between 1982 and 2012). [B] Patients with autoimmune disease who visited the rheumatology department of Sakai City Hospital after Apr. 2014 were screened for achalasia. **[Results]** [A] Twelve patients with achalasia were identified (no. 1 - 3). All experienced nocturnal coughing with regurgitation of ingested food without gastric acid and suffered from aspiration pneumonia. Interestingly, all these patients had autoantibodies to scl-70 or centromere. The prevalence of such autoimmune diseases in achalasia patients was 25%(3/12). Inversely, the prevalence of achalasia in SLE patients was estimated at 0.19 % (1/539), while that in SSc patients 0.67 % (2/297). These patients are 19 times and 67 times more likely to suffer from achalasia compared with general population (1/10000), respectively. None of the 153 patients with myositis had achalasia. [B] One patient at Sakai City Hospital (no. 4) was also with both MCTD and achalasia. Patient no.: sex (onset age for achalasia)/ autoimmune disease (onset age) 1: M (69) / SLE (69) 2: F (23) / SSc (54) 3: F (66) / SSc (49) 4: F (43) / MCTD (43) **[Conclusion]** The prevalence of achalasia among patients with autoimmune diseases (especially SSc) is much higher than that in general population. When patients with autoimmune diseases present recurrent regurgitation of food without gastric acid, esophageal achalasia must be ruled out. SSc patients with reflux esophagitis can exhibit similar symptoms. However, their regurgitations are usually with gastric acid. This is an important point.

#### ICW-C5-1

##### Factors associated with the early development of Pneumocystis jirovecii pneumonia among rheumatoid arthritis patients receiving Biological agents

Shin-ichiro Omura, Rei Ito, Toshiaki Miyamoto  
Seirei Hamamatsu General Hospital, Japan

Conflict of interest: None

**[Objectives]** To determine rheumatoid arthritis (RA) patients receiving Biological agents (Bio) who need Pneumocystis jirovecii pneumonia (PCP) prophylaxis, including indications or duration of antimicrobials. **[Methods]** We retrospectively analyzed 16 RA patients who developed PCP during Bio and compared with 262 RA patients who received Bio more than three month and did not developed PCP. **[Results]** For the PCP patients, the median age was 65.5 years old and all patients were receiving concomitant methotrexate (MTX). Five patients (31.3%) were receiving concomitant corticosteroids with Bio. Four patients (25%) had coexisting lung disease and three patients (18.8%) had diabetes mellitus. The median interval between the initiation of Bio and the onset of PCP was 13.8 weeks and fifteen patients (93.8%) developed PCP within 26 weeks after the initiation of Bio. The patients with PCP were significantly older ( $p < 0.05$ ), had co-existing pulmonary diseases and diabetes mellitus ( $p < 0.05$ ), higher rate of peripheral blood lymphocyte counts  $< 1000$  cells/ $\mu$  ( $p < 0.05$ ) than the patients without PCP. However, We have no significant difference the others. Cox proportional hazards analysis revealed that age over 65 years [hazard ratio (HR) 4.15, 95 % confidence interval (CI) 1.49-11.6,  $p = 0.007$ ], coexisting lung disease (HR 2.48, 95 % CI 0.79-7.79,  $p = 0.118$ ), diabetes mellitus (HR 6.70, 95 % CI 1.84-24.4,  $p = 0.004$ ), and peripheral blood lymphocyte counts less than 1000 cells/ $\mu$  (HR 5.44, 95 % CI 2.0-14.8,  $p = 0.001$ ) were significant risk factors for PCP. Moreover, Kaplan-Meier estimates showed that PCP developed more frequently in patients with two or more risk factors than in other patients ( $p < 0.001$ ). **[Conclusion]** We must consider the possibility of PCP for the first 26weeks in RA patients receiving Bio and may consider making PCP prophylaxis at least for the first 26weeks particularly if two or more risk factors are present.

## ICW-C5-2

### A cut-off value analysis of decreased ratio of lymphocyte counts for the onset of *Pneumocystis pneumonia*

Hisayo Horiuchi, Kenta Misaki, Rintaro Saito, Yuri Nakamura, Yoshie Gon, Takumi Nagamoto, Hiroataka Yamada, Toshihiko Yokota  
Department of Endocrinology and Rheumatology, Kurashiki Central Hospital, Okayama, Japan

Conflict of interest: None

[Objectives] *Pneumocystis pneumonia* (PCP) is a life-threatening infection caused by *Pneumocystis jirovecii*, essentially occur in immunocompromised individuals. However, it is not clear which immunocompromised non-HIV infected patients should be given prophylaxis. Here, we elucidate the decrease ratio of lymphocyte counts as a contributing risk factor for the onset of PCP in immunocompromised hosts. [Methods] Twenty patients with PCP who received prednisolone (PSL), DMARDs or Biologics were enrolled from September 1984 to February 2013 in Kurashiki Central Hospital. Patient were classified as follows: Group1: received only PSL (mean PSL:  $27.0 \pm 5.4$  mg/day) (n=13). Group2: received PSL with DMARDs or Biologics (mean PSL:  $8.4 \pm 2.9$  mg/day) (n=7). Control group: non-PCP patients received only PSL without PCP prophylaxis (mean PSL:  $16.5 \pm 2.5$  mg/day) (n=13). Statistically, there is no significant differences about the dosage of PSL between Group1 and control group (p=0.36). The decrease ratio of the lymphocyte counts between just before receiving the immunosuppressants and at the onset of PSP ( $\Delta$ Lym) were calculated in each group. [Results] Primary diseases were CTD (n=14), non-CTD (n=6) in Group1 and 2. CTD (n=13) were selected as a control group in a random matter. Mean $\Delta$ Lym in Group 1, 2 and Control group were  $80.5 \pm 4.3\%$ ,  $62.6 \pm 4.2\%$  and  $33.5 \pm 8.0\%$ , respectively. The mean $\Delta$ Lym in Group1 was significantly decreased compared with those of in control group ( $80.5\%$  vs  $33.5\%$ ; p<0.0001). In ROC analysis, the cut-off value of  $\Delta$ Lym for the onset of PCP in the patients who received only PSL was 60.9% (sensitivity: 92.3%, specificity: 92.3%, odds ratio: 144.0). [Conclusion]  $\Delta$ Lym might be a new risk factor and an index parameter for the indication for prophylaxis of PCP.

## ICW-C5-3

### Plasma Presepsin as Biomarker of Systemic Bacterial Infection in Patients with Systemic Autoimmune Diseases

Kohei Tsujimoto<sup>1,2</sup>, Iku Shirasugi<sup>1</sup>, Masashi Taniguchi<sup>1</sup>, Yutaka Shinkawa<sup>1</sup>, Yuya Tabuchi<sup>1</sup>, Mizue Okazaki<sup>1</sup>, Masaaki Fujita<sup>1</sup>, Saori Hatachi<sup>1</sup>, Masato Yagita<sup>1</sup>

<sup>1</sup>Department of Clinical Immunology and Rheumatology, Tazuke Kofukai Foundation, Medical Research Institute, Kitano Hospital, Osaka, Japan, <sup>2</sup>Department of Infectious Diseases, Tazuke Kofukai Foundation, Medical Research Institute, Kitano Hospital, Osaka, Japan

Conflict of interest: None

[Objectives] This study aimed to assess the diagnostic and prognostic value of plasma presepsin levels for patients with autoimmune disease, to distinguish those with a bacterial infection from those with a disease flare. [Methods] Plasma levels of presepsin (P-SEP), procalcitonin (PCT), C-reactive protein (CRP), and the white blood cell (WBC) counts were determined in 54 patients diagnosed with systemic autoimmune disease. Patients were divided into two groups: 14 patients in the infection group and 40 patients in the disease flare group. [Results] The mean age of the 54 patients (13 men and 41 women) was 61.5 years (median: 67 years; range: 18 to 83 years). The plasma levels of P-SEP were >2-fold higher in the bacterial infection group ( $469.0 \pm 121.2$  pg/mL) than in the disease flare group ( $183.5 \pm 25.89$  pg/mL). The PCT levels were >4-fold higher in the bacterial infection group ( $0.39 \pm 1.26$  ng/mL) than in the disease flare group ( $0.09 \pm 0.017$  ng/mL). In contrast, there was no significant difference in CRP, WBC or creatinine level. [Conclusion] This is the first study to provide evidence that measurements of plasma P-SEP may distinguish autoimmune disease patients admitted for flares or bacterial infection.

## ICW-C5-4

### Clinical course of non-tuberculous mycobacterial (NTM) infection in patients with rheumatic diseases

Sayaka Takenaka<sup>1</sup>, Yuki Fujisaza<sup>1</sup>, Sumie Nakahashi<sup>1</sup>, Kennosuke Mizushima<sup>1</sup>, Hideki Ito<sup>1</sup>, Ayako Hirata<sup>1</sup>, Takehisa Ogura<sup>1</sup>, Hideto Kameda<sup>1</sup>, Keisuke Izumi<sup>2</sup>, Hisaji Oshima<sup>2</sup>

<sup>1</sup>Department of Rheumatology, Toho University, Japan, <sup>2</sup>Department of Rheumatology, Natural Hospital Organization Tokyo Medical Center, Japan

Conflict of interest: None

Objective: To pursue a better management of patients with rheumatic diseases complicated by NTM infection. Methods: Among 7013 patients with rheumatic diseases visiting Ohashi Medical Center and Tokyo Medical Center, 20 patients were enrolled in this study by meeting the diagnostic criteria of NTM infection by The Japanese Society for Tuberculosis and The Japanese Respiratory Society, and being followed-up for more than 1 year. The medical records of enrolled patients were retrospectively reviewed. Results: Eleven patients with rheumatoid arthritis, 4 patients with vasculitis, 3 patients with Sjogren's syndrome and 1 patient with dermatomyositis and systemic lupus erythematosus for each. Bronchiectasis was observed in 13 patients. Three patients (2 with Sjogren's syndrome and 1 with microscopic polyangiitis) showed the radiographic aggravation of NTM disease, all of whom were female patients infected by *Mycobacterium avium* complex (MAC), having been treated with low-dose macrolide monotherapy. MAC was detected in 11 patients, *M. chelonae* in 2 patients and *M. abscessus* in 1 patient, and undetermined in 3 patients among those with stable NTM diseases. The number of patients with active rheumatic diseases was 9 at the diagnosis of NTM, and it decreased to 4 at the last observation by altering/intensifying therapies for rheumatic diseases. Conclusion: For patients with active rheumatic diseases complicated by NTM infection, both an adequate control of rheumatic disease activity and the combination chemotherapy, if needed, for NTM infection should be highly considered.

## ICW-C5-5

### Biological agents did not increase the risk of nontuberculous mycobacterium infection in rheumatoid arthritis patients: a retrospective single center study

Hiroshi Takei, Naoshi Nishina, Katsuya Suzuki, Kunihiro Yamaoka, Tsutomu Takeuchi

Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] To investigate the risk of nontuberculous mycobacterium (NTM) infection in rheumatoid arthritis (RA) patients treated with biological agents. [Methods] We retrospectively reviewed the medical records of all RA patients under regular follow up at our institution in December 2012. They were observed through October 2014. NTM was diagnosed according to the criteria proposed by the Japanese Society for Tuberculosis and the Japanese Respiratory Society. This study included 1649 patients. Thirty-four patients were diagnosed as NTM; 27 had already been diagnosed as NTM at the time of inclusion and 7 were newly diagnosed during observation period. The prevalence rate and incidence rate of NTM in RA patients was 1637 per  $10^5$  patients and 250 per  $10^5$  patient-years, respectively. NTM species included *M. avium* complex in 32 patients, *M. kansasii* in 1 patient, and *M. abscessus* in 1 patient. Of 1615 patients without NTM and of 34 patients with NTM, 827 and 11 patients had been treated with at least 1 biological agent, respectively. Biological agents were not associated with increased risk of NTM (odds ratio (OR) 0.46; 95% confidence interval (CI) 0.22-0.94; p=0.04). After diagnosed as NTM, 12 patients were treated with biological agents; 5 patients by etanercept (ETN); 2 by tocilizumab (TCZ); and 5 by abatacept (ABT). Four of them experienced exacerbation (1 with ETN, 2 with TCZ, and 1 with ABT). Three of the other 22 receiving non-biological therapy also experienced exacerbation (methotrexate, salazosulfapyridine, and tacrolimus, respectively). Biological agents was not associated with exacerbation, either (OR 3.2; 95%CI 0.57-17.5; p=0.21). Respiratory failure and death was not detected during observation period among patients with NTM. [Conclusion] Biological agents did not in-

crease the risk of NTM infection or the exacerbation of NTM. We should be careful when treating RA patients with NTM regardless of therapy.

### ICW-C5-6

#### Seasonal fluctuations of the activity of rheumatoid arthritis under treatment of biologic agents

Bunki Natsumoto, Hirofumi Shoda, Shoko Tateishi, Hiroko Kanda, Keishi Fujio, Kazuhiko Yamamoto  
Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Conflict of interest: None

**Background:** The seasonal fluctuations in the disease activity of rheumatoid arthritis (RA) have been reported. However, consensus has not been obtained about which factors lead to the seasonal fluctuations. **Method:** A retrospective cohort study was conducted among RA patients attending to biologic outpatient clinic of the University of Tokyo Hospital. The values of average  $\Delta$ DAS (variance from the average DAS) of all the patients in each month were calculated. The risk factors associated with fluctuation of  $\Delta$ DAS were analyzed by bi- and multivariate analyses. **Result:** A total of 210 RA patients were eligible. Significant difference of DAS scores was observed between those in July ( $\Delta$ DAS = +13%) and those in February ( $\Delta$ DAS = -8%) ( $P = 0.0062$ ).  $\Delta$ DAS of the patients evaluated in the July 2013 showed significant correlation with air pressure 3 to 7 days before the evaluation, HAQ and rainfall in bivariate analysis ( $P < 0.05$ ). Air pressure 4 days before the evaluation was significantly associated with  $\Delta$ DAS in the multivariate analysis ( $P = 0.017$ ). **Conclusion:** We demonstrated the seasonal fluctuation of the disease activity of bio-treated RA patients. Disease activity exacerbated in summer and was mainly influenced by air pressure.

### ICW-C6-1

#### Value of Trabecular Bone Score as a Predictor for Future Fractures in Rheumatoid Arthritis Patients

Dam Kim<sup>1,2</sup>, Soo-Kyung Cho<sup>1,2</sup>, Ji Young Kim<sup>3</sup>, Yun Young Choi<sup>3</sup>, Yoon-Kyoung Sung<sup>1,2</sup>

<sup>1</sup>Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea, <sup>2</sup>Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, <sup>3</sup>Department of Nuclear Medicine, Hanyang University Hospital, Seoul, Korea

Conflict of interest: None

**[Objectives]** Previous vertebral fracture (VF), low bone mineral density (BMD) and high risk by fracture risk assessment (FRAX) are powerful predictors for future fracture in rheumatoid arthritis (RA) patients. We conducted this study to identify the role of trabecular bone score (TBS) on predicting future fracture in RA patients by comparing with other predictors. **[Methods]** One hundred female RA patients aged 50 years or more were enrolled in this study. Prevalent VFs defined as moderate to severe degree VFs, TBS obtained with the TBS iNsight software, L-spine BMD by dual-energy X-ray absorptiometry, and the 10-year possibility of major osteoporotic fracture calculated by FRAX were collected. Since we regarded that prevalent VF was the strongest predictor for future fracture, patients were divided into two groups by presence of VFs. Accuracy to detect the VF was assessed by determining the area under the receiving operator characteristics (ROC) curve, and Pearson correlations were used to identify the linear relationship between TBS, L-spine BMD and FRAX. **[Results]** Twenty six patients (26%) in 100 patients revealed to have VF. L-spine BMD was not different between two groups ( $0.83 \pm 0.15$  g/cm<sup>2</sup> with VF vs.  $0.84 \pm 0.15$  g/cm<sup>2</sup> without VF,  $p = 0.85$ ) whereas TBS was significantly lower in patients with VFs ( $1.28 \pm 0.07$  vs.  $1.34 \pm 0.09$ ,  $p < 0.01$ ). The areas under curves (AUCs) were 0.683, 0.518 and 0.818 for TBS, L-spine BMD and FRAX, respectively. Among patients who were taking glucocorticoids ( $n = 57$ ), the AUCs were 0.758, 0.448 and 0.762 for TBS, L-spine BMD and FRAX, respectively. There was a modest negative correlation between TBS and FRAX ( $r = -0.370$ ,  $p < 0.01$ ), while there was no correlation between TBS and L-spine BMD ( $r = -0.061$ ,  $p = 0.56$ ). **[Conclusion]** TBS and FRAX showed modest correlation, and had higher accuracy to detect the patients with VFs than BMD among RA patients especially with glucocorticoids. Therefore, TBS could be a useful tool for

predicting future fracture in RA patients.

### ICW-C6-2

#### Comparative re-fracture rates in hospitals with and without a fracture liaison service: a 6 month historical cohort study

Ayano Nakayama, Gabor Major, Nikolai Bogduk  
John Hunter Hospital, Newcastle, NSW, Australia

Conflict of interest: None

**Objective:** To evaluate the effectiveness of the fracture liaison service (FLS) at John Hunter Hospital. **Methods:** All patients aged  $\geq 50$  years with a minimal trauma fracture between 01/07/2010 and 31/12/2010 at John Hunter Hospital (FLS hospital) were compared to patients at Liverpool Hospital (no FLS hospital). The hospital computer system was used to collect information on baseline patient characteristics (age, gender, baseline fracture site) as well as re-fracture rates and death rates in a 3 year follow up period. **Results:** 527 patients at John Hunter Hospital and 416 patients at Liverpool Hospital were included in the study. Over 3 years, 65/527 (12%) patients at John Hunter Hospital and 70/416 (17%) patients at Liverpool Hospital had a minimal trauma re-fracture. Unexpectedly there were more deaths in the follow up period at John Hunter hospital (135/527, 26%) compared with Liverpool Hospital (60/416, 14%). 103/527 (20%) patients at John Hunter Hospital were seen at the fracture liaison service. All patients were analyzed in an intention-to-treat analysis regardless of whether they were seen in the fracture liaison clinic. The mortality data will be checked against NSW death and birth registries for accuracy. Final statistical analysis with adjustments for baseline characteristics and death as a competing risk for re-fracture will be undertaken. **Conclusions:** The unadjusted data from the study shows a re-fracture benefit but is unable to demonstrate a mortality benefit at John Hunter Hospital. Further analysis of adjusted data and discussion of results are to follow.

### ICW-C6-3

#### The response of osteocytes to infection following total hip replacement

Masakazu Kogawa, L. Bogdan Solomon, Caroline Moran, Renee T. Ormsby, Kunihiro Hosaka, David M. Findlay, Gerald J. Atkins

Centre for Orthopaedic and Trauma Research, University of Adelaide, Adelaide, Australia

Conflict of interest: None

**[Objectives]** Total hip replacement (THR) is a principal surgical procedure for patients with advanced osteoarthritis (OA). However, bacterial infection following surgery can result in prosthesis loosening and the need for revision surgery. Bacterial infections quickly activate innate immune responses, leading to local migration of neutrophils and the release of pro-inflammatory cytokines, some of which are known to stimulate osteoclast formation and activity. In addition, osteoblasts are known to be a significant line of defense against colonisation by bacteria and bacterial formation of biofilms. However, the effect of these infections on the osteocyte, which plays key roles in the regulation of physiological bone remodelling by controlling other cell types in bone, remains unclear. In this study, we have begun to address this. **[Methods]** Bone samples were collected from age-matched patients undergoing either revision THR for orthopaedic implant-related infection ( $n = 16$ ) or THR for primary OA ( $n = 47$ ), with informed written patient consent. Small samples of bone were collected with a trephine needle from the acetabulum prior to reaming and from the iliac wing as a control. Bone samples were rinsed in PBS and homogenized for the extraction of total RNA and the analysis of gene expression by real-time RT-PCR. **[Results]** Our analysis of these samples has revealed the acetabular bone of the infected group has significantly increased expression of the osteocyte-related gene SOST mRNA in comparison to the primary OA group. The RANKL/OPG mRNA expression ratio, and IL1 $\beta$  and TWEAK mRNA levels were higher in infected group. SOST mRNA levels correlated with TWEAK and TLR2 mRNA in the infected but not in the primary OA cohort. Interestingly, SOST mRNA and RANKL/OPG ratio remained higher after antibiotic treatment. **[Conclusion]** These results suggest that in the situation of infection, sclerostin may play a role in implant loosening through actions on osteocytes.

## ICW-C6-4

### The incidence of bisphosphonate-related beaking (atypical femoral incomplete fracture) in patients with autoimmune diseases taking glucocorticoid; from the longitudinal study of 2 years

Naoki Kondo<sup>1</sup>, Hiroe Sato<sup>2</sup>, Yoko Wada<sup>2</sup>, Takeshi Nakatsue<sup>2</sup>, Takeshi Kuroda<sup>3</sup>, Junichi Fujisawa<sup>1</sup>, Masaaki Nakano<sup>4</sup>, Ichiei Narita<sup>2</sup>, Naoto Endo<sup>1</sup>

<sup>1</sup>Division of Orthopaedic Surgery, Department of Regenerative and Transplant Medicine, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, <sup>2</sup>Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, <sup>3</sup>Niigata University Health Administration Center, Niigata, Japan, <sup>4</sup>Department of Medical Technology, School of Health Sciences, Faculty of Medicine, Niigata University, Niigata, Japan

Conflict of interest: None

[Objective] It has been shown that long-term use of bisphosphonates (BPs) is associated with atypical femoral fracture (AFF) by inhibiting not only bone resorption but also bone formation. Focal lateral cortical thickening is defined as “beaking”, which is the initial sign of AFF. We studied longitudinally the incidences of beaking and of complete AFF in patients with autoimmune diseases taking bisphosphonate for prophylaxis of glucocorticoid-induced osteoporosis. [Methods] Bilateral anterior-posterior femoral X-ray were surveyed in 125 autoimmune diseases patients (70 in SLE, 16 in RA, 9 in MCTD, 30 in the others). Beaking was detected in each case and the incidences were examined on day 0 and 2 years after the entry, respectively. In addition, the incidences of prodromal thigh pain and complete AFF were evaluated. The mean age was 54 years old (19 to 84), and the mean disease duration was 13.3 years (1 to 43.7). All subjects were taking prednisolone (10 mg/day on average, 0.5 to 25mg). Duration of bisphosphonate treatment was 4.9 years on average (0.5 to 12 years). [Results] The incidence of beaking was 8 % (10 cases 15 limbs) on day 0, and 10% (12 cases 21 limbs) 2 years after the entry, respectively. In 2 cases, beaking appeared on the contralateral side. In 2 cases 4 limbs, beaking newly appeared. The incidence of prodromal pain was 1.6% (2 cases) and it did not change 2 years after the entry. Most beaking was detected in subtrochanteric region (about 80%). Complete AFF was detected in 1 case (0.8 %). [Conclusion] The incidence of bisphosphonate-related beaking in autoimmune diseases patients taking glucocorticoid was exclusively high compared to that in primary osteoporosis patients from the previous report (2% from Vieira LR et al, 2012). In particular, the incidence itself was elevated by 2 % after 2 years. In most cases the lesions progressed asymptotically. Then X-ray follow up of bilateral femora is strongly recommended to prevent complete AFF.

## ICW-C6-5

### The Use of Denosumab (Prolia) in the Treatment of Difficult Osteoporotic Cases

Ronald Tan

Society for Healthy Aging Research and Education (SHARE), Hong Kong

Conflict of interest: None

**OBJECTIVE:** The usual treatment of osteoporosis with NSAID's, analgesics, calcium + Vitamin D supplement, calcitonin, strontium ranelate; oral bisphosphonates, or a combination of these requires a prolonged period of time and patients' compliance. Denosumab may be a simpler treatment alternative. **METHOD:** 17 females: mean average 74.23 years; 2 males: mean average 64 years with known T-score > -1.5 + one nonfragility fracture; or T-score of > -2.5 by DEXA Scan were used as criteria for the study. Denosumab 60 mg s.c. q6months or longer with Calcium lactate 600 mg + Vitamin D 400 IU were given: naive patients (3) [15.79%], previously treated: (16) [84.21%]. The patients and physician assessed whether pain (bone) improved: (1) at rest or on rising; (2) aches and pains with temperature/humidity changes; (3) ADL and (4) exercise pain; q1week. **RESULTS:** 13 [68.42%] noted improvement in all areas: within 6-8 weeks; 4 [21%] showed some improvement within 4 weeks. The physician observed similar changes in 10 [52.63%] in 6 - 8 weeks. 2 [10.53%] patients had 3 injections; 4 [21.05%] patients had 2 injections; 13 [68.42%] patients had one injection of denosumab. No adverse effects were observed. **DISCUSSION AND CONCLUSIONS:** De-

nosumab is a human IgG2 monoclonal antibody with affinity and specificity for human RANKL. Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone. Denosumab can also markedly reduce bone formation rates and the significance of this long-term effective is unknown. Thus there is a concern with denosumab's long-term use and a “Holiday Period” (3 years?) has been suggested. Osteoporosis affects a large proportion of our elderly and the use of denosumab should be considered in some of the more serious cases.

## ICW-C6-6

### Assessment of the effect of 12 months administration of denosumab in patients with rheumatic diseases -Increase of bone mineral density in lumbar spine is negatively correlated with baseline oral prednisolone dose and predicted by decreasing rate of ucOC at 6 months-

Kosuke Ebina<sup>1</sup>, Jun Hashimoto<sup>2</sup>, Makoto Hirao<sup>1</sup>, Keisuke Hagihara<sup>3</sup>, Kenrin Shi<sup>1</sup>, Takaaki Noguchi<sup>1</sup>, Hideki Yoshikawa<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Osaka University, Graduate School of Medicine, Osaka, Japan, <sup>2</sup>Department of Rheumatology, National Hospital Organization, Osaka Minami Medical Center, Osaka, Japan, <sup>3</sup>Department of Kampo Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

Conflict of interest: Yes

[Objectives] The aim of this study is to clarify the effect of 12 months administration of denosumab (DSM) in patients with rheumatic diseases (RD). [Methods] DSM was introduced in 145 RD patients (127 female, 61.5 years old, 95 RA, 28 SLE, 4 dermatomyositis, 4 sarcoidosis, 14 other diseases, 77.2% taking prednisolone (PSL) with average dose 4.3mg, 21.4% taking biologics, lumbar spine (LS) T-score -1.7, femoral neck (FN) T-score -2.2, total hip (TH) T-score -1.9, prior vertebral fracture 1.0, prior treatment; bisphosphonate 63.4%, teriparatide 18.6%, none 16.6%) and followed up for 12 months by monitoring bone mineral density (BMD) and bone metabolism markers. [Results] No clinical fracture was observed during 12 months. BMD increase from baseline to 6→12 months was as follows. LS; 3.0→5.4%, TH; 1.6→2.6%, FN; 2.0→3.1%. Baseline dose of oral PSL showed negative correlation with baseline value of bone metabolism markers [P1NP ( $r=-0.31$ ,  $p=0.0004$ ), TRACP-5b ( $r=-0.32$ ,  $p=0.0003$ ), ucOC ( $r=-0.42$ ,  $p=0.000004$ )] and BMD increase of LS at 6 months ( $r=-0.27$ ,  $p=0.002$ ) and 12 months ( $r=-0.29$ ,  $p=0.04$ ), and also with TH at 12 months ( $r=-0.39$ ,  $p=0.01$ ). BMD increase of LS at 12 months (%) was positively correlated with baseline value of bone metabolism markers [P1NP ( $r=0.51$ ,  $p=0.001$ ), TRACP-5b ( $r=0.50$ ,  $p=0.001$ ), ucOC ( $r=0.54$ ,  $p=0.001$ )] and their decreasing rate at 6 months [TRACP-5b ( $r=0.37$ ,  $p=0.02$ ), ucOC ( $r=0.53$ ,  $p=0.003$ )]. Multivariate logistic regression analysis with a forward stepwise procedure revealed significant indicator of LS BMD change at 12 months was decreasing rate of ucOC at 6 months ( $\beta=0.50$ , 95%CI=-0.13 - -0.03,  $p=0.005$ ). [Conclusion] Our findings indicate that BMD increasing effects of 12 months DSM administration in RD is significantly correlated with baseline bone metabolism turnover which is suppressed by baseline oral PSL dose-dependently. In addition, BMD increase of LS at 12 months is strongly predicted by decreasing rate of ucOC at 6 months.

## ICW-C6-7

### Assessment of the effect of 6 months administration of denosumab in patients with primary osteoporosis -Increase of bone mineral density in femoral neck is significantly higher in combination with active vitamin D compared to native vitamin D-

Kosuke Ebina<sup>1</sup>, Jun Hashimoto<sup>2</sup>, Makoto Hirao<sup>1</sup>, Kenrin Shi<sup>1</sup>, Takaaki Noguchi<sup>1</sup>, Hideki Yoshikawa<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Graduate School of Medicine, Osaka University, Osaka, Japan, <sup>2</sup>Department of Rheumatology, National Hospital Organization, Osaka Minami Medical Center, Osaka, Japan

Conflict of interest: Yes

[Objectives] The aim of this study is to clarify the effect of 6 months

administration of denosumab (DSM) in patients with primary osteoporosis (PO). [Methods] DSM was introduced in 102 PO patients [98 female, 76.4 years old, 64 with active and 38 with native vitamin D, lumbar spine (LS) T-score -2.8, femoral neck (FN) T-score -2.6, total hip (TH) T-score -2.4, P1NP 63.5 ug/l, TRACP-5b 416.6 mU/dl, ucOC 7.3 ng/ml, intact-PTH 42.3 pg/ml, prior vertebral fracture 2.3, prior treatment; bisphosphonate (BP) 48.0%, teriparatide (TPTD) 36.3%, none 13.7%], and followed up for 6 months by monitoring bone mineral density (BMD) and bone metabolism markers. [Results] BMD increase from baseline to 6 months was as follows. LS (Total 4.1% / TPTD 4.0% / BP 4.2% / none 4.2%), TH (Total 2.6% / TPTD 2.4% / BP 2.1% / none 5.1%), and FN (Total 3.7% / TPTD 2.3% / BP 2.0% / none 5.6%). None-treatment group tend to show highest increase in BMD, although not significant. Vulnerable fractures of 2 lumbar spine and 2 proximal femur were observed during 6 months treatment (3 fractures in BP group and 1 LS fracture in TPTD group). Factors affecting 6 months BMD increase were investigated, and BMD increase in FN was significantly high in combination with active vitamin D compared to native vitamin D (4.8% v.s. -0.5%;  $p=0.002$ ). Although not significant, there was same tendency in LS (4.5% v.s. 3.1%) and TH (3.1% v.s. 2.0%) BMD increase. In addition, the changing rate of intact-PTH at 6 months was significantly low in active vitamin D compared to native vitamin D (-1.2% v.s. 29.1%;  $p=0.04$ ), and there was no significant correlation between the difference of vitamin D and the change of bone metabolism markers. [Conclusion] Our findings indicate that 6 months administration of DSM is more effective when combined with active vitamin D compared to native vitamin D, especially in increasing FN BMD of patients with primary osteoporosis.

### ICW-C7-1

#### Previous anemia and risk of postoperative adverse events in patients with systemic lupus erythematosus

Chien-Chang Liao<sup>1,2</sup>, Ta-Liang Chen<sup>1,2</sup>

<sup>1</sup>School of Medicine, Taipei Medical University, Taipei, Taiwan, <sup>2</sup>Department of Anesthesiology, Taipei Medical University Hospital, Taipei, Taiwan

Conflict of interest: None

[Objectives] Factors associated with postoperative complications and mortality in patients with SLE was not completely understood. This study evaluated whether previous anemia is a risk factor for adverse outcomes after surgery in patients with SLE. [Methods] With the use of reimbursement claims from the Taiwan's National Health Insurance system, we performed a population-based cohort study of 8164 patients with SLE undergoing major surgeries. Postoperative complications and mortality were compared between surgical patients with and without history of anemia. The multivariate logistic regression was performed to calculate odds ratios (ORs) and 95% confidence intervals (CIs) of adverse events associated with anemia in patients with SLE after adjusted for sociodemographics and coexisting medical conditions. [Results] Among surgical patients with SLE, patients with previous anemia had higher risks of postoperative septicemia (OR 1.37, 95% CI 1.03-1.84), pneumonia (OR 1.82, 95% CI 1.23-2.69), stroke (OR 1.95, 95% CI 1.23-3.08), and acute renal failure (OR 1.66, 95% CI 1.00-2.73) compared with those without anemia. Preoperative anemia was also associated with 30-day in-hospital mortality (OR 4.23, 95% CI 2.47-7.27) in patients with SLE. Patients with anemia also had longer mean of length of stay (15.6 vs. 10.2 days,  $p<0.0001$ ) and higher mean of medical expenditure (5534 vs. 3405 US dollars,  $p<0.0001$ ) after surgery. [Conclusion] Among patients with SLE, preoperative anemia may be a risk factor for postoperative adverse events, such as complications, mortality, prolonged length of stay, and increased medical expenditure.

### ICW-C7-2

#### Joint and Tendon Involvement in Patients with Early Systemic Lupus Erythematosus in Comparison with Early Rheumatoid Arthritis: an ultrasound study of hands and wrists

Takehisa Ogura, Ayako Hirata, Hideki Ito, Sayaka Takenaka, Sumie Nakahashi, Kennosuke Mizushina, Rie Kujime, Munetsugu Imamura, Norihide Hayashi, Yuki Fujisawa, Hideto Kameda

Division of Rheumatology, Toho University Ohashi Medical Center, Tokyo, Japan

Conflict of interest: None

[Objectives] Although both systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) may lead to the joint deformity, different characteristics such as the absence or the presence of bone destruction have been recognized as well. We aimed to clarify the difference of joint and tendon involvement between SLE and RA patients by using ultrasonography (US). [Methods] Thirteen SLE and 32 RA patients were selected from the treatment-naïve patients with joint symptoms, visiting Toho University Ohashi Medical Center between January 2011 and March 2014. Enrolled patients had at least one swollen or tender joint. The wrist, metacarpophalangeal and proximal interphalangeal joints and related extensor/flexor tendons were ultrasonographically examined from both palmar and dorsal sides. Their joints and tendons including tendon sheaths were evaluated using a gray-scale (GS) for synovial thickening and synovial fluid retention, and power Doppler (PD) for blood flow according to a semiquantitative method based on a scale of grades 0 to 3, and patients graded with  $GS \geq 2$  or  $PD \geq 1$  were judged as having joint synovitis and or tendinitis/tenosynovitis. [Results] Joint synovitis and tendinitis/tenosynovitis were observed in 11 (79%) and 12 (86%) of 13 SLE patients, respectively, and in 31 (91%) and 18 (53%) of 32 RA patients, respectively. Thus, SLE patients had tendinitis/tenosynovitis more frequently ( $p=0.034$ ) as compared with RA, and particularly in the wrist joints ( $p=0.008$ , Table 1). Moreover, the concordance of joint synovitis and tendinitis/tenosynovitis in the same region was less in SLE patients ( $\kappa=0.18$ ) as compared with RA ( $\kappa=0.44$ ). [Conclusion] Joint synovitis was similarly observed ultrasonographically in both SLE and RA patients, while tendinitis/tenosynovitis was more frequently observed in SLE patients than in RA patients. In addition, tenosynovitis in SLE patients may develop rather independently from synovitis.

### ICW-C7-3

#### Efficacy and safety of multi-target therapy using a combination of cyclophosphamide and tacrolimus in patients with refractory lupus nephritis

Ryota Sakai, Akiko Shibata, Kentaro Chino, Tsuneo Kondo, Ayumi Okuyama, Hirofumi Takei, Koichi Amano  
Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Saitama, Japan

Conflict of interest: None

[Objectives] Pulsed cyclophosphamide (pCYC) for lupus nephritis (LN) has limited effects in some cases; mycophenolate mofetil is an off-label pharmaceutical agent in Japan. Multi-target therapy with pCYC and tacrolimus (Tac) was used for treating LN, including refractory cases, at our center (UMIN4893). [Methods] We evaluated 13 patients with active LN. Prednisolone was started at 1 mg/kg/day, aiming to reduce the dose to 10 mg/day after 6 months. Intravenous cyclophosphamide was administered as per the Euro-Lupus protocol (500 mg biweekly for 3 months). The trough concentration of Tac was adjusted to 5–10 ng/ml as per National Health Insurance. Complete remission (CR) was defined as a spot urine protein/creatinine (UPCR) ratio of  $<0.5$  g/gCr and normal eGFR or eGFR improvement as per EULAR/ERA-EDTA recommendations and KDIGO guidelines. [Results] The mean age was 40.3 years (male:female = 1:12); UPCR, 3.4 g/gCr; serum creatinine, 0.97 mg/dl; C3, 40.5 mg/dl; and C4, 4.6 mg/dl. One, seven, and four patients belonged to Classes III, IV, and IV + V, respectively, and one had no data. Nine out of the 13 patients received the treatment protocol; 4 patients withdrew. The CR at 6 months was 76.9% ( $n = 10/13$ ). Side effects, including infections, did not increase as compared with pCYC therapy, except a transient increase in serum creatinine with Tac. [Conclusion] Multi-target therapy such as pCYC and Tac can be a therapeutic option for refractory LN.

### ICW-C7-4

#### Transition of renal prognosis in 148 patients with lupus nephritis in single center retrospective analysis

Eri Katsuyama<sup>1</sup>, Ken-ei Sada<sup>1</sup>, Takayuki Katsuyama<sup>1</sup>, Haruki Watanabe<sup>1</sup>, Mariko Narazaki<sup>1</sup>, Noriko Toyota Tatebe<sup>1</sup>, Koichi Sugiyama<sup>1</sup>, Katsue Sunahori Watanabe<sup>1</sup>, Hiroshi Wakabayashi<sup>1</sup>, Tomoko Kawabata<sup>1</sup>, Jun Wada<sup>1</sup>, Hirofumi Makino<sup>2</sup>

<sup>1</sup>Department of Medicine and Clinical Science, Okayama University



Conflict of interest: None

[Objectives] The standard induction and maintenance therapies for lupus nephritis (LN) has been established by the advent of corticosteroids and immunosuppressive agents. We investigated their impacts on the prognosis of LN over recent decades. [Methods] We conducted a retrospective cohort study of the patients with LN. We divided enrolled 148 patients into 4 groups (group 1 (n=32: 1990-1996), group 2 (n=40: 1997-2001), group 3 (n=33: 2002-2007) and group 4 (n=43: 2008-2013)) according to the period of renal biopsy. We compared clinical characteristics and renal survival among these 4 groups. Primary end point was defined as increase of serum creatinine (s-Cr) by 1.5-folds from baseline. [Results] S-Cr levels at the baseline became lower overtime (1.00, 0.96, 0.87, and 0.80 mg/dl) while the proportion of ISN/RPS class IV was not declined (78%, 50%, 76%, and 51%) in group 1 to 4, respectively. Of 148 patients, 10 (6.8%) patients reached the end point within 5 years. The renal survivals were not differ among 4 groups (log rank test, p=0.86). [Conclusion] Although the histological diagnosis was attempted at lower s-Cr levels in recent years, the renal outcome has not been substantially improved. We should modify and improve the standard therapies to obtain better renal outcomes.

### ICW-C7-5

#### The impact of mini-pulse steroid and anticoagulants during embryo transfer on systemic lupus erythematosus or antiphospholipid syndrome patients undergoing *in vitro* fertilisation

Cheng-Hsun Lu<sup>1</sup>, Song-Chou Hsieh<sup>2</sup>

<sup>1</sup>Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, National Taiwan University Hospital Yun-Lin Branch, Yunlin, Taiwan, <sup>2</sup>Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

Conflict of interest: None

[Objectives] Patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) can have fertility problems. These patients undergoing *in vitro* fertilisation (IVF) might suffer disease flares, resulting in dissatisfied IVF result. We report our experience in facilitating IVF process in patients with SLE or APS who had prior IVF failure probably caused by immunological factors. [Methods] This retrospective study reviewed infertility patients who was admitted to the rheumatology ward preceding embryo transfer (ET) procedures over the period 2010 to 2012 at National Taiwan University Hospital. The inclusion criteria were: (1) diagnosis of SLE (American College of Rheumatology classification criteria) or APS (Sydney criteria), and (2) previous IVF failure related to autoimmune disorders. [Results] Six women were admitted preceding ET in the total of 7 cycles of IVF. Their diagnosis was: SLE (n=1), SLE with antiphospholipid antibodies (n=1), and APS (n=4). All of them received methylprednisolone mini-pulse therapy in addition to baseline medications, and prompt administering of low-molecular-weight heparin (LMWH) if any suspicion of thrombosis or elevated serum level of D-dimer was detected. They had undergone 24 cycles of IVF before, of which 23 cycles failed; the only successful pregnancy (4%) lead to spontaneous abortion at 28 weeks of gestational age. However, with treatments of steroid mini-pulse therapy and LMWH during ET in a hospital setting, then the 7 cycles of IVF achieved 4 successful implantations (57%), and 3 gave birth to live babies (43%). In addition, during the follow-up, no major disease flare happened. [Conclusion] This preliminary result shows that intensive monitoring of disease activity and preemptive mini-pulse steroid as well as LMWH therapies during ET may improve pregnancy outcomes in infertility patients with SLE or APS who had previous IVF failures associated with immune factors and undergoes IVF again.

### ICW-C7-6

#### Predictors of pulmonary arterial hypertension (PAH) and its long-term outcomes in patients with systemic lupus erythematosus (SLE): a single-center cohort study

Qian Wang<sup>1</sup>, Can Huang<sup>1</sup>, Mengtao Li<sup>1</sup>, Yongtai Liu<sup>2</sup>, Xiaoxiao Guo<sup>2</sup>, Jiliang Zhao<sup>1</sup>, Jinzhi Lai<sup>2</sup>, Zhuang Tian<sup>2</sup>, Yan Zhao<sup>1</sup>, Xiaofeng Zeng<sup>1</sup>  
<sup>1</sup>Department of Rheumatology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China, <sup>2</sup>Department of Cardiology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China

Conflict of interest: None

[Objectives] To describe the clinical features and long-term outcomes of SLE-PAH patients and to identify the predictive factors of PAH and its different outcomes. [Methods] A prospective cohort of SLE-PAH was established since 2006. All participants was diagnosed with PAH by right heart catheterization (RHC) and ruling out interstitial pneumonitis and pulmonary thromboembolism. Clinical and laboratory features, SLE activity measurements and outcomes including PAH-related death and achievement of treat-to-target were recorded. Predictors of PAH were identified by multivariate logistic regression by comparing with SLE patients without PAH adjusted with age and gender in 1:4 ratio. Cox hazard proportional regression was used to identify predictors of different outcomes. [Results] 111 RHC-confirmed SLE-PAH patients were enrolled. The duration of SLE at baseline was (5.2±6.0) years. Mean pulmonary arterial pressure detected by RHC was (46.4±11.4) mmHg. 46% of the patients were at WHO function class I or II. All patients received immunosuppressive treatment and 65% were also treated with PAH vasodilators. The independent risk factors (P <0.001) for PAH were: SLE duration, pericarditis, anti-u<sub>1</sub>RNP antibody, anti-SSA antibody (P =0.003), SLE disease activity index (SLEDAI) ≤9. The 3-year survival rate was 81.3%. Right atrial pressure (RAP) elevation (>5mmHg) was independent risk factor of PAH-related death (HR 7.767, P =0.017). Hypocomplementemia (HR 4.692, P =0.007), early diagnosed PAH by RHC (<6 months) (HR 4.859, P =0.007), and CI≥2.5 L/(min×m<sup>2</sup>) (HR 4.290, P =0.013) were independent predictors for achievement of treat-to-target. [Conclusion] SLE patients with longer duration, pericarditis, anti-u<sub>1</sub>RNP and SSA antibody, lower SLEDAI are at higher risk of PAH. Elevation of RAP in SLE-PAH may imply a poor long-term survival, and patients with increased SLE activity, reserved heart function and received prompt diagnostic procedure at early stage of PAH have optimal response to treatment.

### ICW-C8-1

#### Predictors of therapeutic outcomes in patients with Takayasu arteritis

Shoichi Fukui<sup>1</sup>, Sosuke Tsuji<sup>1</sup>, Masataka Umeda<sup>1</sup>, Ayako Nishino<sup>1</sup>, Yoshikazu Nakashima<sup>1</sup>, Takahisa Suzuki<sup>1</sup>, Yoshiro Horai<sup>1</sup>, Tomohiro Koga<sup>1</sup>, Shin-ya Kawashiri<sup>1,2</sup>, Naoki Iwamoto<sup>1</sup>, Kunihiro Ichinose<sup>1</sup>, Yasuko Hirai<sup>1</sup>, Mami Tamai<sup>1,2</sup>, Hideki Nakamura<sup>1</sup>, Tomoki Origuchi<sup>1,3</sup>, Atsushi Kawakami<sup>1</sup>

<sup>1</sup>Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, <sup>2</sup>Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, <sup>3</sup>Department of Health Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Conflict of interest: None

[Objectives] Takayasu arteritis (TA) is a rare autoimmune vasculitic disorder which predominantly affects young women. The aim of this study is to identify clinical features as the predictors of relapses and usage of biologics agents in patients with TA. [Methods] We retrospectively analyzed 25 patients with TA in Nagasaki university hospital from April in 2003 to March in 2014. They were all newly diagnosed TA patients which could be followed up at least 6 months. We analyzed the baseline variables, laboratory data, clinical symptoms and therapeutic outcomes after treatments and the prognostic factors using medical records. [Results] Of the one male and 24 female (96%), 11 patients (44%) had relapses after starting treatments. The median age at TA onset was 37.1 years old. Eleven patients (44%) were HLA-B52 positive. The fever and general fatigue at onset were commonly seen in the relapse group

( $p < 0.05$  and  $p < 0.01$ , respectively). Their median erythrocyte sedimentation rate (ESR) was 57.3 mm/hr vs. 89.7 mm/hr in the relapse group ( $p < 0.05$ ). The median total cholesterol (TChol) was 192 mg/dL vs. 142 mg/dL in the relapse group ( $p < 0.05$ ). Multivariate analysis showed that general fatigue at onset and TChol  $< 150$  mg/dl were predictors of relapse (Odds ratio (OR): 19.1, 95%CI: 1.68-218 and OR: 11.6, 95%CI: 1.03-131, respectively). There were no predictors for usage of biologics agents. The younger onset ( $p < 0.05$ ), presence of a carotid bruit ( $p < 0.05$ ) and aortic regurgitations ( $p < 0.01$ ) were associated with HLA-B52 positive patients. [Conclusion] We found that general fatigue at onset and hypocholesterolemia are predictors of relapse in TA patients. HLA-B52 positive patients may have risk of disease onset at younger age, presence of a carotid bruit and aortic regurgitations. Our findings may indicate that TA patients with hypocholesterolemia at onset are needed aggressive therapies to avoid TA relapses.

## ICW-C8-2

### The significance of temporal artery biopsy in patients with giant cell arteritis

Takayuki Katsuyama<sup>1</sup>, Ken-ei Sada<sup>1</sup>, Yoshia Miyawaki<sup>1</sup>, Keiji Ohashi<sup>1</sup>, Michiko Morishita<sup>1</sup>, Eri Katsuyama<sup>1</sup>, Haruki Watanabe<sup>1</sup>, Mariko Narazaki<sup>1</sup>, Noriko Toyota Tatebe<sup>1</sup>, Koichi Sugiyama<sup>1</sup>, Katsue Sunahori Watanabe<sup>1</sup>, Hiroshi Wakabayashi<sup>1</sup>, Tomoko Kawabata<sup>1</sup>, Jun Wada<sup>1</sup>, Hirofumi Makino<sup>2</sup>

<sup>1</sup>Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, <sup>2</sup>Okayama University Hospital, Okayama, Japan

Conflict of interest: None

[Objectives] Giant cell arteritis (GCA) is a large and medium-sized blood vessel systemic vasculitis, and the ACR 1990 criteria are widely used. The usefulness of computed tomography (CT), magnetic resonance image (MRI) and positron emission tomography CT (PET-CT) in the diagnostic procedure has called an attention and the temporal artery biopsy (TAB) is still an essential component for diagnosis. [Methods] We analyzed 21 patients who were diagnosed with GCA between January 2008 and October 2014 to compare the usefulness of image analyses and biopsy in the patients with GCA. [Results] The mean age of patients was  $69.5 \pm 8.2$  years. The positive rate of abnormal findings of each test was as follow; color duplex sonography: 29%(2/7), CT scan: 65%(13/20), MRI: 8%(1/12) and PET-CT 59%(10/17). TAB detected abnormal findings in 47%(7/15) of patients with GCA. The comparison between the patients with and without abnormal findings of TAB failed to detect significant differences in clinical backgrounds or response to treatment. The patients with abnormal findings of TAB tended to show higher rate of abnormal PET-CT findings than those with normal result of TAB (80% vs. 29%,  $p = 0.071$ ), while similar rate of abnormal CT findings (71% vs. 63%,  $p = 0.714$ ). In 4 patients with normal results of CT scan and PET-CT, 1 patient showed the abnormal findings of TAB. On the other hand, we experienced that a patient with microscopic polyangiitis showed abnormal CT findings in temporal artery but only arteriosclerotic hyperplasia was found by TAB. Thus we confirmed that TAB was the significant examination for both definite and differential diagnosis of GCA. [Conclusions] Positive rate of TAB ranges from 10 to 40% in different reported series. The algorithm to predict the result of TAB was proposed recently. Although TAB is invasive procedure with low positive rate, some cases required TAB to diagnose or exclude GCA.

## ICW-C8-3

### Hallmarks of exacerbation of interstitial lung disease in ANCA-associated vasculitis

Haruki Watanabe<sup>1</sup>, Ken-ei Sada<sup>1</sup>, Yosuke Asano<sup>1</sup>, Keiji Ohashi<sup>1</sup>, Yoshia Miyawaki<sup>1</sup>, Michiko Morishita<sup>1</sup>, Eri Katsuyama<sup>1</sup>, Takayuki Katsuyama<sup>1</sup>, Mariko Narazaki<sup>1</sup>, Noriko Toyota Tatebe<sup>1</sup>, Koichi Sugiyama<sup>1</sup>, Katsue Sunahori Watanabe<sup>1</sup>, Hiroshi Wakabayashi<sup>1</sup>, Tomoko Kawabata<sup>1</sup>, Jun Wada<sup>1</sup>, Hirofumi Makino<sup>2</sup>

<sup>1</sup>Medicine and Clinical Science, Okayama University Graduate School of Medicine Dentistry and Pharmaceutical Sciences, Okayama, Japan, <sup>2</sup>Okayama University Hospital, Okayama, Japan

Conflict of interest: None

[Objectives] Japanese nationwide prospective cohort study revealed high prevalence of interstitial lung disease (ILD) in the patients with ANCA-associated vasculitis (AAV). But it is still unknown whether ILD is a complication or a symptom of AAV. We conducted the retrospective study to elucidate factors associated with exacerbation of interstitial lung disease in patients with ANCA-associated vasculitis. [Methods] The medical records of 23 newly diagnosed AAV patients with ILD at Okayama university hospital were retrospectively reviewed over a period of 2 years, from 2006-2013. ILD was diagnosed by high resolution CT of lung. We excluded the patients without the repeated CT examinations after 6-month therapeutic intervention. The extent of honeycombing and reticular pattern was evaluated for up to 2 years. [Results] Mean age was 68.7 years and 14 were females. Of those, 14 patients classified as microscopic polyangiitis, 3 were classified as granulomatous polyangiitis, and 6 were not classifiable. All patients were MPO-ANCA positive. ILD exacerbated in 6 patients (26%). The levels of KL-6 at baseline was significantly higher (862 vs. 378 U/ml,  $p = 0.014$ ) and BVAS at baseline significantly lower (17.3 vs. 11.2,  $p = 0.047$ ) among the patients with exacerbated ILD than those without exacerbated ILD. The patients with exacerbated ILD tended to receive additional treatment for the disease activity such as general and cutaneous symptoms other than pulmonary manifestations (50 vs 12 %,  $p = 0.051$ ). [Conclusion] ILD may be treatment target as a symptom of AAV.

## ICW-C8-4

### Retrospective analysis of patients with a novel Japanese variant of multicentric Castleman's disease associated with anasarca and thrombocytopenia; TAFRO syndrome

Yasufumi Masaki, Hironori Shimizu, Tomomi Sato, Takuji Nakamura, Akio Nakajima, Haruka Iwao, Miyuki Miki, Tomoyuki Sakai, Takafumi Kawanami, Yoshimasa Fujita, Masao Tanaka, Toshihiro Fukushima Hematology and Immunology, Medicine, Kanazawa Medical University, Kahoku, Ishikawa, Japan

Conflict of interest: None

[Objectives] Multicentric Castleman's disease (MCD) is a polyclonal lymphoproliferative disorder that manifests as hypergammopathy and severe inflammation. Recently, A unique Japanese variant of MCD having thrombocytopenia, anasarca, fever, reticuline fibrosis/renal dysfunction, and organomegaly, a constellation called TAFRO syndrome have been proposed recently. [Methods] Clinicopathologic data on 37 patients with TAFRO syndrome and similar symptoms were analyzed retrospectively. [Results] The patients enrolled in this study were likely to have a combination of thrombocytopenia, ascites, pleural effusions, anemia, fever, myelofibrosis, renal dysfunction, and organomegaly. Lymphadenopathy was generally mild, less than 1.5 cm in diameter, with histopathological evidence of mixed or less hyaline vascular type MCD. Autoantibodies were sometimes detected, but this disease did not fulfill the diagnostic criteria for any autoimmune diseases. Although glucocorticoids, immunosuppressant, and tocilizumab were effective in some patients, others showed clinical deterioration despite treatment. [Conclusion] TAFRO syndrome is still rare, making multicenter clinical surveys necessary to reach a consensus regarding its diagnostic criteria, therapeutic strategies, and pathophysiological etiology.

## ICW-C8-5

### Familial Juvenile Idiopathic Arthritis: Identification of a genetic risk factor for monogenic form of systemic onset subtype

Sulaiman M Al-Mayouf  
King Faisal Specialist Hospital and Research Center, King Abdulaziz University Hospital, Riyadh, Saudi Arabia

Conflict of interest: None

Objective To identify the cause of an autosomal recessive form of Systemic onset JIA (So-JIA) Methods Out of 32 siblings with familial JIA, we identified 14 siblings with So-JIA from 5 consanguineous families followed at KFSHRC, Riyadh. All patients met ILAR criteria for So-JIA. Clinical data reviewed and compared with sporadic cases. We used linkage homozygosity mapping and whole exome sequencing to identify the disease associated gene and mutation. Results Mean age at onset

was 3.2 years; all patients had polyarthritis and associated systemic features. Patients had progressive disease course with erosive arthritic changes. All patients had inadequate response to intensive treatment including biologic agents. Linkage analysis localized So-JIA to a region on chromosome 13 with a maximal LOD score of 11.33 at *rs9567217*. Whole exome sequencing identified a homoallelic missense mutation in LACC1 encoding the enzyme laccase domain containing 1. The mutation was confirmed by Sanger sequencing and segregated with disease in all 5 families based upon an autosomal recessive pattern of inheritance and complete penetrance. Conclusion We provide strong genetic evidence of a monogenic autosomal recessive form of So-JIA associated with mutation of *LACC1*. It is likely that this represents a subset of So-JIA.

## ICW-C9-1

### Role of nailfold videocapillaroscopy in diagnosis and evaluation of Chinese systemic sclerosis patients

Xu Dong, Zheng Yuanfang, Li Mengtao, Hou Yong, Wang Qian, Zeng Xiaofeng

Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China

Conflict of interest: Yes

[Objectives] To evaluate the performance of the new 2013 ACR/EULAR classification criteria for SSc in clinical practice, and to explore the potential correlation of the scores for nailfold videocapillaroscopy (NVC) parameters and the clinical manifestations. [Methods] Patients diagnosed with SSc clinically were prospectively recruited. Diagnosis of SSc was based on the evaluation of two experienced rheumatologists. Patients diagnosed with other connective diseases were recruited as disease control, and healthy adults as healthy control. Enlarged and giant capillaries, haemorrhages, capillary number, disorganisation of the microvascular array, and capillary ramifications were the evaluated semiquantitative parameters with NVC test. [Results] 93 SSc patients, 58 other connective diseases and 15 healthy were recruited. 65 patients in 93 SSc patients and 2 patients in 58 other connective diseases fulfilled the old criteria, and 88 and 3 patients respectively fulfilled the new criteria. The sensitivity of the 2013 criteria (95%, 95%CI 90%~99%) is better than the 1980 criteria (70%, 95%CI 60%~79%) ( $P=0.000$ ). There is no significant difference between the specificity of the two criterias (95%, 95%CI 89%~100% and 97%, 95%CI 92%~100% respectively,  $P=1.000$ ). In SSc patients, there were significant correlations between the following parameters and the clinical manifestations: 1. capillary number decrease and Rodnan scores ( $p=0.001$ ), RP ( $p=0.000$ ), digital ulcers ( $p=0.000$ ), telangiectasis ( $p=0.006$ ), myositis ( $p=0.038$ ), and PAH ( $p=0.023$ ). 2. Irregularly enlarged capillaries and Rodnan scores ( $p=0.046$ ), RP ( $p=0.000$ ), digital ulcers ( $p=0.010$ ), myositis ( $p=0.028$ ). 3. Haemorrhages and stomach involvement ( $p=0.007$ ). 4. Disorganisation of the vascular array and Rodnan scores ( $p=0.010$ ), RP ( $p=0.000$ ), digital ulcers ( $p=0.007$ ), telangiectasis ( $p=0.026$ ). [Conclusion] The new criteria showed increased sensitivity and same specificity. NVC is a useful tool in evaluation of the severity of the disease.

## ICW-C9-2

### Verifying practical effectiveness of the 2013 ACR/EULAR classification criteria for systemic sclerosis (SSc) using Nailfold videocapillaroscopy (NVC) in Japanese patients

Yurie Sato<sup>1</sup>, Satoshi Kubo<sup>1</sup>, Kazuhisa Nakano<sup>1</sup>, Shingo Nakayamada<sup>1</sup>, Shunsuke Fukuyo<sup>1</sup>, Ipppei Miyagawa<sup>1</sup>, Yasuyuki Todoroki<sup>1</sup>, Kazuyoshi Saito<sup>1</sup>, Shin Tanaka<sup>3</sup>, Minoru Satoh<sup>2</sup>, Yoshiya Tanaka<sup>1</sup>

<sup>1</sup>The First Department of Internal Medicine, University of Occupational and Environment Health, Kitakyusyu, Japan, <sup>2</sup>Department of Clinical Nursing, University of Occupational and Environmental Health, Kitakyushu, Japan, <sup>3</sup>Department of Human Information and Life Sciences, University of Occupational and Environmental Health, Kitakyushu, Japan

Conflict of interest: None

[Objectives] The criteria for SSc were newly revised in 2013 by the ACR/EULAR for the first time in past 33 years. Of note, evaluating nailfold capillary abnormalities by NVC were included in the criteria. NVC

is a non-invasive and safe technique that is reported to have both diagnostic and prognostic value, and widely accepted in Europe. Although in Japan, evaluating capillary abnormalities of SSc by NVC is not widely recognized and its effectiveness in Japanese patient had never been studied. We here validated the new criteria in Japanese patients with using NVC. [Methods] 69 patients of our hospital with Raynaud phenomenon were enrolled. We evaluated if they satisfy 1980 ACR criteria, 2003 Japanese criteria or 2013 ACR/EULAR criteria, and calculated their sensitivity and specificity. The definitive diagnosis was made by skin biopsy. [Results] Sensitivity of 2013 ACR/EULAR criteria were higher (87.0%) than those of 1980 ACR criteria (65.2%) and 2003 Japanese criteria (71.7%). The 7 cases were diagnosed as SSc by new criteria, but not by previous criteria. Although these cases did not have sclerodactyly, they showed puffy fingers and capillary abnormalities like giant capillaries and microhemorrhages, which are the earliest NVC findings in SSc patients. On the contrary, capillary abnormalities were not detected in cases such as primary Raynaud's syndrome. Specificity of these three criteria was comparable (87.0%). [Conclusion] In Japanese patients, the 2013 ACR/EULAR criteria for SSc also performed high sensitivity and specificity and should allow for more patients to be classified correctly as SSc. Especially, NVC can provide the early diagnosis of SSc before skin sclerosis progress. Clinical application of NVC and its epidemiological studies in Japanese patient are required.

## ICW-C9-3

### Reliability of the qualitative nailfold videocapillaroscopy (NVC) assessment in a systemic sclerosis cohort (SCOPE study)

Satoshi Kubo<sup>1</sup>, Kazuhisa Nakano<sup>1</sup>, Shingo Nakayamada<sup>1</sup>, Shintaro Hirata<sup>1</sup>, Shunsuke Fukuyo<sup>1</sup>, Ipppei Miyagawa<sup>1</sup>, Yurie Sato<sup>1</sup>, Yasuyuki Todoroki<sup>1</sup>, Kazuyoshi Saito<sup>1</sup>, Shin Tanaka<sup>3</sup>, Minoru Satoh<sup>2</sup>, Yoshiya Tanaka<sup>1</sup>

<sup>1</sup>The 1st Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, <sup>2</sup>Department of Clinical Nursing, University of Occupational and Environmental Health, Kitakyushu, Japan, <sup>3</sup>Department of Human Information and Life Sciences, University of Occupational and Environmental Health, Kitakyushu, Japan

Conflict of interest: None

[Objectives] The Classification Criteria for Systemic Sclerosis (SSc) including NVC findings were published by ACR/EULAR. However, there are no fully validated outcome measures for SSc activity. The aim of this study is to evaluate the reliability of the scoring system based on NVC images as an index of SSc disease activity. [Method] 55 SSc patients were assessed by qualitative NVC scoring. Fibrosis was evaluated in each biopsy specimen by  $\alpha$ -SMA immunohistochemistry. The clinical features were evaluated by organ involvement score defined by Ministry of Health, Labour and Welfare Japan. [Results] Active NVC score (Enlarged capillaries, Giant capillaries, Hemorrhages) and chronic NVC score (Loss of capillaries, Disorganization of the vascular array, Ramification) were detected in SSc patients. Grading these score into 4 stages (normal, early, active, late), these stages reflected the degree of pathological skin fibrosis. Moreover, active NVC scores were correlated with m-Rodnan skin score, while chronic NVC scores were correlated with not only m-Rodnan skin score but also renal- and entero- dysfunctions. Among chronic NVC scores, the ramification scores that indicate the most advanced stage were correlated with the severity of pulmonary hypertension. On the other hand, early NVC stage was more prevalent in patients with anti-centromere antibody, while late NVC stage was more prevalent in patients with anti-Scl-70 antibody. [Conclusion] In SSc, capillaries become enlarge, concomitantly hemorrhages and capillary reductions occur, and neoangiogenesis with ramified capillaries are induced. NVC images in SSc patients reflected these developments, organ manifestation and autoantibodies, indicating a putative role of NVC scores as index of SSc disease activity.

## ICW-C9-4

### Left Ventricular Morphological, Functional Abnormalities and Myocardial Characteristics in Systemic Sclerosis without Cardiac Symptoms, Using Cardiac Magnetic Resonance Imaging: A prospective pilot study

Kaita Sugiyama, Hitomi Haraoka, Yosuke Nagasawa, Atsuma Nishiwaki,

Natsumi Ikumi, Takamasa Nozaki, Hirotake Inomata, Hidetaka Shiraiwa, Hiromi Karasawa, Noboru Kitamura, Mitsuru Iwata, Yoshihiro Matsukawa, Masami Takei  
Division of Hematology and Rheumatology, Nihon University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] Systemic sclerosis (SSc) is associated with an increased prevalence of cardiac involvement despite often being clinically silent. Cardiac magnetic resonance imaging (CMR) is useful since it focuses on late gadolinium enhancement (LGE) abnormalities, ventricular morphology, and function. Our study aimed to analyze CMR and investigate the association between CMR findings and brain natriuretic peptide (BNP) in SSc patients (pts) without cardiac symptoms. [Methods] 35 consecutive female pts with SSc (mean age, 56 years) without cardiac symptoms as well as 20 matched controls (mean age, 55 years) were underwent non contrast or contrast enhanced CMR. Left ventricular (LV) function was measured using LV ejection fraction (EF). LV morphology was measured by absolute LV mass index (LVMI)/end-diastolic volume (EDV). Serum BNP levels were measured in all subjects. LGE was obtained to assess myocardial fibrosis. Myocardial inflammation was assessed with black blood T2-WI. [Results] Comparison with the control group, SSc group showed significant higher EDV with tendency of high LVMI. T2-WI imaging was detected in 6 of 35 pts (17%). LGE was detected in 16 of 35 SSc pts (46%). There was no difference in EF among the control group, SSc with LGE (+) and LGE (-) group. LVMI was significant higher in the LGE (+) group than in the LGE (-) group. 48% of LGE (+) group showed concentric or eccentric hypertrophy. The BNP level of the SSc group was significantly higher than controls. BNP levels were significantly correlated with LVMI in the SSc group. Adjustment for age, disease duration and BNP, LGE (+) group did not modified in LVMI. [Conclusion] SSc pts without cardiac symptoms have a high prevalence of cardiac abnormalities comparing matched controls. SSc patients with LGE showed abnormal morphology associated with LVMI and serum BNP, leading to cardiac remodeling with possible development of cardiac involvement, even with normal EF.

### ICW-C9-5

#### Anti-MDA5 autoantibody: Clinical significance in U.S. patients with amyopathic and myopathic dermatomyositis

Siamak Moghadam-Kia<sup>1</sup>, Chester V. Oddis<sup>1</sup>, Shinji Sato<sup>2</sup>, Masataka Kuwana<sup>3</sup>, Rohit Aggarwal<sup>1</sup>

<sup>1</sup>Department of Medicine, Division of Rheumatology and Clinical Rheumatology, University of Pittsburgh, Pittsburgh, U.S.A, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Tokai University, School of Medicine, Isehara, Japan, <sup>3</sup>Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan

Conflict of interest: None

**Objectives:** To determine the association of anti-MDA5 antibody with interstitial lung disease (ILD), rapidly-progressive ILD (RPILD) and outcome in U.S. patients with clinically amyopathic and classic dermatomyositis (CADM and DM, respectively). **Methods:** CADM patients were identified in the University of Pittsburgh Myositis Database and 1:1 matched (gender and age) to DM controls. Anti-MDA5 was measured by serum ELISA on both groups. RPILD was defined by the acute onset and rapid worsening of dyspnea or severe radiographic ILD within 3 months from the onset of respiratory symptoms. Kaplan-Meier, log-rank, and Chi-square tests were used for analysis. **Results:** We identified 61 CADM patients (female 62%; mean age 48.2) and 61 DM controls (female 64%; mean age 44.8). The frequency of anti-MDA5 positivity, ILD, and RPILD were similar in two cohorts (MDA5+: CADM: 13.1% [8/61], DM: 13.1% [8/61]; ILD+: CADM: 31.1% [19/61], DM: 26.2% [16/61]; RPILD+: CADM: 8.2% [5/61], DM: 5% [3/61]; p = NS). Anti-MDA5 positivity was significantly associated with ILD as 50% (8/16) of MDA5+ subjects had ILD vs. 25.5% (27/106) of MDA5- subjects (p=0.04). Anti-MDA5 was strongly associated with RPILD (p<0.001). Among 8 anti-MDA5+ patients with ILD, 7 had RPILD leading to early death in 5; whereas, only one MDA5- patient had RPILD (1/106). Among 8 anti-MDA5+ patients with ILD, baseline pulmonary functions testing variables were available in 3 (FVC% 48, 30, 41, and FEV1% 57, 37, 54, re-

spectively) which were worse compared to the anti-MDA5- patients with ILD (mean FVC% 79, mean FEV1% 84; N=18). Anti-MDA5 positivity was significantly associated with poor survival (p=0.007). Multivariate analysis suggested that anti-MDA5 positivity was predictive of survival even after controlling for diagnosis, age at diagnosis, gender, ethnicity, smoking, and ILD (p=0.002). **Conclusion:** Anti-MDA5 antibody is significantly associated with ILD, RPILD, worse pulmonary function, and survival in US DM and CADM patients.

### ICW-C9-6

#### Randomized, Double-Blind, Placebo-Controlled Phase 3 Studies (FUTURE 1 and 2) of Secukinumab in treatment of Active Psoriatic Arthritis

Iain B McInnes<sup>1</sup>, Hiroyuki Fujita<sup>2</sup>, Philip Mease<sup>3</sup>, Shephard Mpofo<sup>4</sup>, The FUTURE Study Groups

<sup>1</sup>Institute of Infection, Immunity and Inflammation, University of Glasgow, Scotland, UK, <sup>2</sup>Novartis Pharma K.K., Japan, <sup>3</sup>Swedish Medical Center and University of Washington, USA, <sup>4</sup>Novartis Pharma AG, Switzerland

Conflict of interest: Yes

[Objectives] To assess efficacy and safety of secukinumab (SEC), a human anti-IL-17A monoclonal antibody, in patients (pts) with Psoriatic Arthritis (PsA), in placebo (PBO)-controlled phase 3 studies (FUTURE 1 and 2). [Methods] FUTURE 1: Pts on SEC received 10 mg/kg i.v. at week (wk) 0, 2, and 4, followed by 75 mg s.c. (IV→75 mg) or 150 mg s.c. (IV→150 mg) every 4 wks. PBO was given on the same schedules. FUTURE 2: Pts received SEC (300, 150 or 75 mg) s.c. or PBO at wk 0, 1, 2, 3, 4 and then every 4 wks. The primary end point in both studies was American College of Rheumatology 20 (ACR 20) response at wk 24. Secondary endpoints included PASI 75/90, Disease Activity Score 28 using C-reactive protein (DAS28-CRP), Short Form-36 Physical Component Summary (SF-36 PCS), Health Assessment Questionnaire-Disability Index (HAQ-DI), ACR 50, dactylitis and enthesitis. FUTURE 1 also assessed radiographic progression using the van der Heijde modified total Sharp score (mTSS). [Results] FUTURE 1: Both IV→75 mg and IV→150 mg demonstrated significantly higher ACR 20 responses vs. PBO at wk 24 (50.5% and 50.0% vs. 17.3%, p<0.0001). At wk 24, SEC significantly inhibited radiographic disease progression vs. PBO (changes in mTSS: 0.02, 0.13 vs 0.57, p<0.05). FUTURE 2: At wk 24, ACR 20 responses were significantly greater with SEC groups than PBO: 54.0%, 51.0%, 29.3% vs. 15.3%, with SEC 300, 150, 75 mg vs. PBO (p<0.0001 for SEC 300 and 150 mg; p<0.05 for SEC 75 mg). ACR 50/70 responses were 35.0/20.0%, 35.0/21.0%, 18.2/6.1%, and 7.1/1.0% for SEC 300, 150, 75 mg vs. PBO, respectively. SEC 300 and 150 mg also improved dactylitis and enthesitis vs. PBO (p<0.05). SEC was well tolerated with no unexpected safety findings. [Conclusion] SEC demonstrated rapid and clinically significant improvements in the signs and symptoms of active PsA and inhibited radiographic progression.

## International Concurrent Workshop Basic

### ICW-B1-1

#### SH3BP2 Cherubism Mutation Potentiates TNF-Induced Osteoclastogenesis Via NFATc1 and TNF-Mediated Inflammatory Bone Loss

Tomoyuki Mukai<sup>1,2</sup>, Yoshitaka Morita<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Kawasaki Medical School, Kurashiki, Japan, <sup>2</sup>Department of Oral and Craniofacial Sciences, School of Dentistry, University of Missouri-Kansas City, Kansas City, USA

Conflict of interest: None

[Objectives] SH3 domain-binding protein 2 (SH3BP2) is a signaling adapter protein which regulates immune and skeletal systems. SH3BP2 gain-of-function mutations have been reported to be responsible for a genetic disease cherubism (OMIM#118400). Cherubism is characterized by excessive jawbone destruction with swelling of the lower face. TNF is expressed in human cherubism lesions, which contain a large number of TRAP-positive multinucleated cells, suggesting that TNF attributes to the excessive jawbone resorption. The purpose of this study was to examine the role of SH3BP2 in TNF-induced osteoclastogenesis and TNF-mediated inflammatory bone loss using the P416R SH3BP2 cherubism mutant (gain-of-function) mice model. [Methods] Primary bone marrow macrophages (BMMs) isolated from wild-type (Sh3bp2<sup>+/+</sup>) and P416R SH3BP2 cherubism mutant knock-in heterozygous (Sh3bp2<sup>KI/+</sup>) mice were cultured with M-CSF (25 ng/ml) and TNF (100 ng/ml) in the absence of RANKL for 4 days. Osteoclast differentiation and function were determined. Intracellular signaling pathways were evaluated by Western blotting. Next, Sh3bp2<sup>KI/+</sup> mice were crossed with human TNF transgenic (hTNFtg) mice. Inflammation and bone loss were examined by clinical inspection and histological and micro-CT analyses. [Results] Sh3bp2<sup>KI/+</sup> BMMs mice were highly responsive to TNF and differentiate into osteoclasts independently of RANKL. The P416R SH3BP2 mutation enhanced the nuclear localization of NFATc1. In the hTNFtg model, the P416R SH3BP2 cherubism mutation did not alter the severity of paw swelling but exacerbates focal and systemic bone loss with increased osteoclast formation. [Conclusion] These findings suggest that the SH3BP2 cherubism mutation can cause jawbone destruction by promoting osteoclast formation in response to TNF. SH3BP2 is a key regulator for TNF-induced osteoclastogenesis and TNF-mediated bone loss.

### ICW-B1-2

#### Pathological significance of osteoclast differentiation in TIARP-deficient mice

Yuko Kurashima<sup>1</sup>, Isao Matsumoto<sup>1</sup>, Asuka Inoue<sup>1</sup>, Naoto Umeda<sup>1</sup>, Yuki Tanaka<sup>1</sup>, Hoshimi Kawaguchi<sup>1</sup>, Hiroshi Ebe<sup>1</sup>, Satoru Takahashi<sup>2</sup>, Takayuki Sumida<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan, <sup>2</sup>Department of Anatomy and Embryology, Doctoral Program in Biomedical Sciences, Eraduate School of Comprehensive Human Sciences, University of Tsukuba, Japan

Conflict of interest: None

[Objectives] TNF $\alpha$ -induced adipose-related protein (TIARP) is a six-transmembrane protein induced by TNF- $\alpha$  and IL-6, and its deficient mice spontaneously develop polyarthritis with bone erosion. Previous studies suggested that TIARP functions as a negative regulator in inflammation via suppressing STAT3 and NF $\kappa$ B activation. However the role of TIARP in inflammatory bone erosion and osteoclast differentiation is mostly unknown. This study aims to elucidate the role of TIARP in osteoclast differentiation. [Methods] 1) Femur from TIARP<sup>-/-</sup> (12 months old) and WT (12 months old) mice were analyzed by micro CT. 2) Bone marrow cells from WT (8 weeks old) mice were cultured with M-CSF and RANKL for 5 days, and TIARP mRNA was assessed by RT-PCR. 3) Bone marrow cells from TIARP<sup>-/-</sup> (8 weeks old) and WT (8 weeks old) mice were cultured with M-CSF and RANKL for 5 days, and osteoclasts were examined by TRAP staining. [Results] 1) TIARP<sup>-/-</sup> mice showed less bone mineral density than WT mice (p<0.05). 2) TIARP mRNA expression was increased after stimulation by RANKL. 3) The numbers of multi-nucleated TRAP-positive cells were significantly higher in bone marrow cells from TIARP<sup>-/-</sup> mice than those from WT mice (p<0.05). [Conclusion] These findings suggest that TIARP suppress inflammatory

bone erosion by inhibiting osteoclastogenesis.

### ICW-B1-3

#### Human dendritic cell-derived osteoclasts have potent bone absorption capacity and antigen-presenting ability

Manabu Narisawa<sup>1</sup>, Satoshi Kubo<sup>1</sup>, Shingo Nakayama<sup>1</sup>, Jidong Zhao<sup>1</sup>, Kei Sakata<sup>2</sup>, Yosuke Okada<sup>1</sup>, Kunihiro Yamaoka<sup>3</sup>, Yoshiya Tanaka<sup>1</sup>

<sup>1</sup>The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, <sup>2</sup>Mitsubishi Tanabe Pharma Corporation, <sup>3</sup>Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] The dendritic cells (DC) as well as monocytes can differentiate into osteoclasts (OC)-like cells in the inflammatory lesions. Dendritic cell-derived osteoclasts (DCOC) may play an important role of joint destructions of rheumatoid arthritis (RA). We investigated differentiation and localization of DCOCs in RA patients. [Methods] Tartrate-resistant acid phosphatase (TRAP) staining was used to detect the location of OC in synovial tissue obtained from RA patients. DCOCs were differentiated from human monocyte-derived DCs. [Results] TRAP positive multinucleated cells were detected in the rheumatoid synovium. Culturing DCs cultured with M-CSF and RANKL resulted in differentiation into DCOCs which were positive of TRAP staining and cathepsin K. In addition, DCOCs expressed major histocompatibility complex (MHC) molecules and costimulatory molecules which were not accompanied in OCs. Furthermore, bone absorption capacity of DCOCs was significantly increased compare with OCs by the evaluation of Pit-formation assay. [Conclusion] Human DCs can differentiate into OC-like cells in the presence of M-CSF and RANKL. DCOCs maintain the expression of costimulatory molecules and show higher bone absorption capacity than OCs. These data suggest that DCOCs have not only potent bone resorption ability but also the antigen-presenting function, and may play an important role in both the maintenance of joint destruction and inflammation in RA.

### ICW-B1-4

#### Differentiation, Function, and Regulation of Human Osteoclast-like Cells Induced by Combination of Tumor Necrosis Factor $\alpha$ and Interleukin 6 from CD14<sup>+</sup> Monocytes

Kazuhiro Yokota, Kojiro Sato, Yoshimi Aizaki, Yasuto Araki, Hiroshi Kajiyama, Yuji Akiyama, Toshihide Mimura

Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Saitama, Japan

Conflict of interest: None

[Objectives] Since local bone destruction associated with rheumatoid arthritis (RA) is partially controllable by biological agents targeting TNF $\alpha$  or IL-6, proinflammatory cytokines may play an important role in the differentiation of bone-resorbing cells. Previously, we reported that mouse osteoclast-like cells (OCLs) with bone resorption activity were induced from bone marrow-derived macrophages by addition of the combination of TNF $\alpha$  and IL-6 both *in vivo* and *in vitro*. Now we examine the differentiation, function, and regulation of human OCLs that were induced by the combination of TNF $\alpha$  and IL-6 from CD14<sup>+</sup> monocytes. [Methods] Human CD14<sup>+</sup> monocytes from peripheral blood were cultured with IL-6, TNF $\alpha$ , or TNF $\alpha$  plus IL-6. The cells were then compared with conventional osteoclasts induced by RANKL. Pit formation assay on dentine slices was performed. The expression levels of NFATc1 were detected by western blot analysis. The effects of osteoprotegerin (OPG), a decoy receptor for RANKL, NFAT inhibitor tacrolimus, or JAK inhibitor tofacitinib were examined. Expression levels of IL-1 $\beta$  mRNA and protein were analyzed by real-time PCR and ELISA, respectively. [Results] The combination of TNF $\alpha$  and IL-6 induced tartrate-resistant acid phosphatase-positive multinucleated OCLs. The differentiation of osteoclasts was inhibited by OPG, whereas that of OCLs was not. OCLs resorbed dentin slices in a manner similar to that of osteoclasts. Stimulated OCLs with TNF $\alpha$  plus IL-6 significantly up-regulated the expression of NFATc1. NFAT inhibitor blocked differentiation of OCLs. The differentiation of OCLs was suppressed by JAK inhibitor, whereas that of osteo-

clasts was not. Expression levels of IL-1 $\beta$  mRNA and protein in OCLs were significantly higher than those in osteoclasts. [Conclusion] Human OCLs differentiated by TNF $\alpha$  plus IL-6, have bone-resorption activity and strongly produce IL-1 $\beta$ . OCLs may contribute to joint destruction in mainly uncontrolled RA.

### ICW-B1-5

#### Dynamic analysis of short-term effects of bisphosphonates by using intravital two-photon microscopy

Junichi Kikuta<sup>1,2</sup>, Masaru Ishii<sup>1,2</sup>

<sup>1</sup>Department of Immunology and Cell Biology, Graduate School of Medicine, Osaka University, Osaka, Japan, <sup>2</sup>Japan Science and Technology Agency, CREST, Tokyo, Japan

Conflict of interest: None

[Objectives] Osteoporosis is frequently observed in patients with rheumatoid arthritis. Bisphosphonates are commonly used for treatment of osteoporosis. There have been many studies about the pharmacological properties of bisphosphonates, but most of them were analyzed by conventional methods such as micro-CT and histological analysis. How bisphosphonates affect dynamics of living mature osteoclasts *in vivo* remains elusive. This study aimed to investigate the short-term effects of bisphosphonates on the function of mature osteoclasts in living bone tissues by using intravital two-photon microscopy. [Methods] We utilized the mice expressing GFP under the promoter of a vacuolar type H<sup>+</sup>-ATPase  $\alpha 3$  subunit that was abundantly expressed in mature osteoclasts ( $\alpha 3$ -GFP mice). By using intravital two-photon microscopy, we observed skull bones of  $\alpha 3$ -GFP mice and visualized fluorescently labeled mature osteoclasts. Risedronate (10  $\mu\text{g}/\text{kg}$ ), alendronate (20  $\mu\text{g}/\text{kg}$ ), or minodronate (4  $\mu\text{g}/\text{kg}$ ), was administered intravenously during imaging, and images were acquired consecutively. [Results] In control condition, we identified different populations of living mature osteoclasts in terms of their motility and function, i.e., 'static – bone resorptive (R)' and 'moving – non resorptive (N)'. Less than 1 hour after injection of risedronate, we found that many static osteoclasts changed their shapes and became moving cells, suggesting R to N functional switching without any change in the total number of osteoclasts. We also found that some osteoclasts had morphological signs suggestive of osteoclast apoptosis after risedronate administration. Furthermore, we could demonstrate that treatment of alendronate or minodronate also induced R to N conversion of osteoclasts on the bone surface. [Conclusion] By visualizing *in vivo* behaviors of mature osteoclasts, we found that bisphosphonates could change osteoclast morphology and inhibit bone resorption in living bone tissues within a short period.

### ICW-B1-6

#### Directly reprogrammed Interleukin-10 producing osteoblast-like cells suppress the osteoclastogenesis and inflammatory response

Kazuki Fujioka<sup>1</sup>, Yuji Kukida<sup>1</sup>, Hidetake Nagahara<sup>1</sup>, Wataru Fujii<sup>1</sup>, Ken Murakami<sup>1</sup>, Takahiro Seno<sup>1,2</sup>, Aihiro Yamamoto<sup>1</sup>, Masataka Kohno<sup>1</sup>, Ryo Oda<sup>3</sup>, Hiroyoshi Fujiwara<sup>3</sup>, Yutaka Kawahito<sup>1</sup>

<sup>1</sup>Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>2</sup>Department of Rheumatic Diseases and Joint Function, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>3</sup>Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: None

[Objectives] Recent progress in the treatment of rheumatoid arthritis enables us to regulate the inflammation, but bone destruction at inflamed joints is a still difficult problem to overcome. Today, it has been reported that somatic cells such as fibroblasts can be converted to other cells (ex. neurons or cardiomyocytes) directly with the transduction of their relating genes. We tried to induce the IL-10 producing osteoblast-like cells (IL-10-iOBs) from fibroblasts as the new therapeutic approach to the inflammation and bone destruction of rheumatoid arthritis. [Methods] We performed the retroviral transfection of genes for IL-10 and Runx2 which was a crucial transcription factor for osteoblast differentiation to mouse fibroblasts, and induced IL-10-iOBs. The characters of these cells were

analyzed with qRT-PCR, ELISA and alizalin red S staining. Next, we added the culture supernatant to Raw264.7 cells and peritoneal macrophages to examine the inhibitory effect for RANKL mediated osteoclastogenesis and LPS induced cytokine expression, respectively. Finally, we transplanted these cells to mouse subcutaneous space, and estimated the mineralization ability *in vivo*. [Results] The IL-10-iOBs strongly expressed osteoblast-specific genes such as osteocalcin and osteopontin. Moreover, these cells massively produced bone matrix that were mineralized by calcium phosphate *in vitro* and *in vivo* without showing tumor-like characteristics. Culture supernatant of IL-10-iOBs contained a great amount of IL-10 and significantly suppressed osteoclastogenesis from RANKL-stimulated Raw264.7 cells as well as LPS-induced production of inflammatory cytokine by macrophages. [Conclusion] The IL-10-iOBs may be applicable to novel cell-based therapy against bone destruction associated with RA.

### ICW-B2-1

#### Excessive Th1 and Th17 cell expansion with abnormal regulatory T cell function in polyarteritis nodosa

Yasuhiro Shimojima<sup>1</sup>, Wataru Ishii<sup>2</sup>, Dai Kishida<sup>2</sup>, Kenichi Ueno<sup>2</sup>, Shuichi Ikeda<sup>2</sup>

<sup>1</sup>Department of Home-Care Promotion, Shinshu University School of Medicine, Matsumoto, Japan, <sup>2</sup>Department of Neurology and Rheumatology, Shinshu University School of Medicine, Matsumoto, Japan

Conflict of interest: None

[Objectives] Polyarteritis nodosa (PAN) is medium-small size necrotizing arteritis. However, immunological etiology is still elusive. In this study, we investigated the kinetic analysis of helper T cells (Th cells) and regulatory T cells (Tregs) in peripheral blood. [Methods] We studied 13 patients with PAN compared with 10 healthy controls (HC) for flow cytometry analysis and functional assay. Intracellular staining of IFN- $\gamma$ , IL-17 and IL-4 in CD4<sup>+</sup> T cells were performed after stimulation with PMA and ionomycin. Circulating Tregs, defined as CD4<sup>+</sup>CD127<sup>low</sup>/CD-25<sup>high</sup>FoxP3<sup>+</sup> T cells, and CTLA-4 expression in CD4<sup>+</sup>CD25<sup>high</sup>FoxP3<sup>+</sup> T cells were simultaneously analyzed. In order to explore the function of Tregs, the proliferation ratio of CD25<sup>-</sup> effector CD4<sup>+</sup> T cells which were co-cultured with Tregs was evaluated after stimulation with anti-CD3/CD28-coupled beads. [Results] In PAN patients, frequencies of Th1 and Th17 cells were significantly elevated in comparison with HC. Higher frequency of Tregs was also shown in PAN, which was correlated with that of Th1. On the other hand, CTLA-4 expression in Tregs from PAN patients was significantly lower. In the functional assay, suppressive ability of Tregs was obviously abrogated in PAN. [Conclusion] Inflammatory pathways mediated by Th cells and disruptive immune tolerance due to dysfunction of Tregs contribute to the development of PAN. In the active phase of PAN, defective Tregs might reactively increase under the environment of higher Th1 expression.

### ICW-B2-2

#### The CD1a+ survivin+ dendritic cell infiltration in the dermis from patients with systemic sclerosis

Sho Mokuda<sup>1,2,3</sup>, Tatsuhiko Miyazaki<sup>4</sup>, Yoshifumi Ubara<sup>5</sup>, Eiji Sugiyama<sup>1</sup>, Kiyoshi Takasugi<sup>3</sup>, Junya Masumoto<sup>6</sup>

<sup>1</sup>Department of Clinical Immunology and Rheumatology, Hiroshima University Hospital, Hiroshima, Japan, <sup>2</sup>Department of Immunology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan, <sup>3</sup>Department of Internal Medicine, Center for Rheumatic Diseases, Dohgo Spa Hospital, Matsuyama, Ehime, Japan, <sup>4</sup>Division of Pathology, Gifu University Hospital, Gifu, Japan, <sup>5</sup>Nephrology Center, Toranomon Hospital, Tokyo, Japan, <sup>6</sup>Department of Pathology, Ehime University Proteo-Science Centre and Graduate School of Medicine, Toon, Japan

Conflict of interest: None

[Objectives] Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis of the skin and other organs, obliterative vasculopathy and immunological abnormalities. Survivin is a member of the inhibitor-of-apoptosis family proteins, and is overexpressed in various cancer cells, while most normal differentiated cells do not express this protein. It

had previously been reported that autoantibodies against survivin were detectable in patients with SSc. However, the pathophysiological relationship between SSc and survivin remains unclear. [Methods] We analyzed the expression of survivin in skin lesions from SSc patients (12 cases) and non-SSc control patients (five cases) with an anti-survivin antibody using immunohistochemistry (IHC). The CD1a, CD207 and CD69 expressions were also investigated in the SSc dermis. [Results] Cells with a high expression of survivin were observed in the SSc dermis. These cells were detected in 66.7% of cases (8/12), while no survivin-expressing cells (0%, 0/5) were detected in the dermis from non-SSc patients ( $p=0.012$ ). Most of the dermal survivin-positive SSc patients had organ derangement (62.5%, 5/8) (three cases of SSc with interstitial pneumonia, one case of SSc with scleroderma renal crisis and one case of SSc with primary biliary cirrhosis), and the survivin-positive rate was higher in these patients than in the SSc patients without organ derangement (0%, 0/4) ( $p=0.038$ ). The survivin-positive cells in the SSc dermis also expressed CD1a, a dendritic cell marker. In addition, some of the CD1a-positive cells also expressed CD207, a Langerhans cell marker. Moreover, CD69, which is expressed in activated lymphocytes, was expressed in the cells around the CD1a-positive dermal cells. [Conclusion] Dermal survivin staining might have potential as a diagnostic marker for SSc with organ derangement. In addition, the CD1a+ survivin+ dendritic cells might contribute to the immunological reaction in SSc dermal lesions.

### ICW-B2-3

#### Feedback Amplification of Skin Fibrosis through Matrix Stiffness Gradient-induced Fibroblast Durotaxis

David Lagares<sup>1</sup>, Fei Liu<sup>2</sup>, Vera Auernheimer<sup>3</sup>, David Adams<sup>4</sup>, Ludovic Vincent<sup>5</sup>, Mohit Kapoor<sup>6</sup>, Melissa Suter<sup>4</sup>, Wolfgang Goldmann<sup>3</sup>, Adam Engler<sup>5</sup>, Daniel Tschumperlin<sup>2</sup>, Andrew M Tager<sup>1</sup>

<sup>1</sup>Pulmonary and Critical Care Unit and Center for Immunology and Inflammatory Diseases, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Massachusetts, USA, <sup>2</sup>Molecular and Integrative Physiological Sciences, Harvard School of Public Health, Boston, USA, <sup>3</sup>Center for Medical Physics and Technology, Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany, <sup>4</sup>Department of Pathology, Massachusetts General Hospital, Boston, USA, <sup>5</sup>Department of Bioengineering, University of California, San Diego, La Jolla, USA, <sup>6</sup>Division of Orthopaedics, The Toronto Western Research Institute, Toronto Western Hospital, The University Health Network (UHN), Toronto Ontario, Canada

Conflict of interest: None

**Objectives** Tissue stiffening, previously thought to just be a consequence of fibrotic diseases, has been recently shown to contribute to their pathogenesis. The molecular mechanisms through which increased tissue rigidity drives disease progression remain to be fully elucidated. **Methods** We have used atomic force microscopy (AFM) to characterize the “topography”, i.e. the spatial distribution, of alterations in matrix stiffness produced in the bleomycin-induced skin scleroderma mouse model. **Results** We consistently found that stiffness, rather than being uniformly elevated in fibrotic tissues, rises and falls in spatial gradients between “peaks” and “valleys.” We hypothesize that the stiffness “peaks” are areas in which the fibrotic process was initiated, or “nucleated”, and that these focal increases in stiffness activate local fibroblasts to myofibroblasts in a process we term “*fibronucleation*”. We further hypothesize that once fibrosis is nucleated, the stiffness gradients leading to these fibrotic peaks are amplified by fibroblast “durotaxis,” – directed migration of cells from regions of lower to higher stiffness. Using hydrogels that recapitulate the stiffness gradients observed in animal fibrosis models, we showed durotaxis of dermal fibroblasts in time-lapse microscopy studies. To prove that fibronucleation occurs in a mouse model of skin fibrosis *in vivo*, we showed the formation of nucleated areas of peak stiffness associated with surrounding stiffness gradients in the dermis by using polarization-sensitive optical coherence tomography (PS-OCT) to construct 3D birefringence maps. We hypothesize that PS-OCT birefringence is increased by augmented collagen crosslinking, and hence reflects increased tissue stiffness. Consistent with our hypotheses, a-SMA+ myofibroblasts localized to areas of high birefringence. **Conclusion** Our study suggests that targeting fibroblast durotaxis has potential to be a new therapeutic strategy for the treatment of scleroderma fibrosis.

### ICW-B2-4

#### CD146 is a receptor for canonical Wnt and promotes fibrosis in the murine model of systemic sclerosis

Lingling Zhang<sup>1</sup>, MengTao Li<sup>1</sup>, Yongting Luo<sup>2</sup>, Zhenzhen Wu<sup>2</sup>, Xiyun Yan<sup>2</sup>, Xiaofeng Zeng<sup>1</sup>

<sup>1</sup>Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China, <sup>2</sup>Key Laboratory of Protein and Peptide Pharmaceuticals, National Laboratory of Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China

Conflict of interest: None

[Objectives] CD146 is an adhesion molecular that belongs to a subgroup of the immunoglobulin superfamily. Previous reports demonstrated that CD146 regulates angiogenesis and inflammation cell infiltration. However, little known about the role of CD146 in fibrosis. Here, we determined whether CD146 contributes to the development of dermal fibrosis. [Methods] Biopsy samples of skin from SSc patients and healthy control subjects were used for immunohistochemistry to determine the expression pattern of CD146. To determine whether CD146 is a mediator of dermal fibrosis, CD146 deficient mice and anti-CD146 monoclonal antibodies were used in the bleomycin-induced dermal fibrosis model. *In vitro* studies with dermal fibroblasts were used to determine the mechanisms by which CD146 contributes to the development of tissue fibrosis. [Results] CD146 was upregulated on dermal fibroblasts and endothelial cells in SSc skin compared to the normal skin. CD146-knockout mice injected with bleomycin had markedly attenuated dermal fibrosis, as quantified by measurements of skin thickness ( $266\pm 10.3$  vs  $431.3\pm 14.4\mu\text{m}$ ), collagen levels ( $261.6\pm 37.1$  vs  $359.9\pm 47.3$   $\mu\text{g}/\text{mg}$ ), myofibroblast accumulation ( $5.6\pm 0.7$  vs  $9.4\pm 0.3/\text{HP}$ ) in lesional skin as compared to the skin of wild-type mice. In addition, anti-CD146 mAb decreased fibrosis at various time points in the bleomycin-induced dermal fibrosis model. *In vitro* studies demonstrated that CD146 is a receptor for Wnt1/ Wnt10b to regulate canonical Wnt signaling. Furthermore, CD146 extracellular domain 4-5 is required for the binding to Wnt1, and Wnt1 promotes CD146 and Dvl2 interaction. Moreover, CD146 deletion or blocked by AA98 was associated with Wnt/ $\beta$ -catenin activation. Importantly, CD146 is essential for Wnt/ $\beta$ -catenin induced fibroblast migration, proliferation and fibration. [Conclusion] These results indicate that CD146 is a mediator of dermal fibrosis and suggest that CD146 may be a therapeutic target in SSc.

### ICW-B2-5

#### Autotaxin is over-expressed in systemic sclerosis (SSc) skin, mediates dermal fibrosis via IL-6, and is a target for SSc therapy

Flavia V Castelino<sup>1</sup>, Gretchen Bain<sup>2</sup>, Lance Goulet<sup>2</sup>, Robert Lafyatis<sup>3</sup>, Andrew M Tager<sup>1</sup>

<sup>1</sup>Massachusetts General Hospital, Harvard Medical School, Boston, USA, <sup>2</sup>PharmAkea Pharmaceuticals, San Diego, USA, <sup>3</sup>Boston University Medical Center, Boston, MA, USA

Conflict of interest: None

[Objectives] Autotaxin (ATX) produces the lipid mediator, lysophosphatidic acid (LPA). We studied the role of ATX in mediating SSc skin fibrosis via LPA and IL-6, utilizing the bleomycin (BLM) mouse model and skin biopsy samples from SSc and healthy subjects. Additionally, we targeted ATX pharmacologically with a novel ATX inhibitor, PAT-048 in this model. [Methods] The subcutaneous BLM model was performed in C57Bl/6 mice for 3, 7, 14 and 28 days and skin ATX was measured by qPCR and ELISA. PAT-048 (20mg/kg oral daily) was administered with BLM for 28 days, or initiated at 7 or 14 days after BLM. Dermal thickness was measured with H&E sections, and collagen was quantified by hydroxyproline measurement. LPA-induced ATX expression was tested on human dermal fibroblasts transfected with IL-6 siRNA. Additionally, healthy and SSc dermal fibroblasts were stimulated with LPA and IL-6 *in vitro*, and IL-6 and ATX induction was evaluated by ELISA, respectively. ATX expression was measured in SSc and healthy subjects skin by qPCR and IL-6 expression was evaluated by immunohistochemistry. [Results] ATX was increased at Day 3 after BLM (3-fold increase,  $p=0.05$ ) suggesting an early role in skin fibrosis. PAT-048 treatment attenuated BLM-

induced dermal fibrosis in all treatment groups (50% reduction, Day 28,  $p=0.01$ ), and reduced IL-6 expression. LPA-induced ATX expression was attenuated with siRNA knock-down of IL-6 (65% reduction,  $p<0.05$ ) in healthy dermal fibroblasts. SSc fibroblasts demonstrated increased LPA-induced IL-6 expression, and increased IL-6-induced ATX expression, compared to healthy fibroblasts suggesting an autocrine ATX/LPA/IL-6 loop. Furthermore, ATX and IL-6 expression were increased in SSc skin ( $n=7$ ) compared to healthy controls ( $n=5$ ; 3-fold increase,  $p=0.006$ ;  $p=0.001$ ) [Conclusion] ATX has a key role in SSc fibrosis and mediates fibrosis in an autocrine loop via LPA and IL-6. Targeting ATX may be an effective new therapeutic strategy for SSc fibrosis.

## ICW-B2-6

### Genetic effect of ABCG2 is stronger than environmental effects for hyperuricemia progression

Akiyoshi Nakayama<sup>1</sup>, Hirotaka Matsuo<sup>1</sup>, Tatsuo Hosoya<sup>2</sup>, Kimiyoshi Ichida<sup>3,4</sup>, Nariyoshi Shinomiya<sup>1</sup>

<sup>1</sup>Department of Integrative Physiology and Bio-Nano Medicine, National Defense Medical College, Saitama, Japan, <sup>2</sup>Department of Pathophysiology and Therapy in Chronic Kidney Disease, Jikei University School of Medicine, Tokyo, Japan, <sup>3</sup>Department of Pathophysiology, Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan, <sup>4</sup>Division of Kidney and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] Gout/hyperuricemia is a common multifactorial disease having typical environmental risks. Recently, common dysfunctional variants of ABCG2, which encodes high-capacity urate exporter, are revealed to be a major cause of gout/hyperuricemia. We then investigated the influence of two dysfunctional variants of ABCG2, Q126X (rs72552713) and Q141K (rs2231142), on serum uric acid (SUA) levels as compared with other risk factors. [Methods] ABCG2 were genotyped with 5,005 Japanese participants of the J-MICC Shizuoka Study. We calculated the population-attributable risk percent (PAR%) of ABCG2 dysfunction and other risk factors for hyperuricemia. A multiple regression analysis was then performed for 4,857 individuals, who were not under treatment for gout/hyperuricemia among 5,005 participants, to evaluate the relationship among SUA levels, ABCG2 dysfunction, and other risk factors. [Results] ABCG2 dysfunction was observed in 53.3% of the population investigated. The PAR% of ABCG2 dysfunction for hyperuricemia was 29.2%, which was much higher than that of the other risks, i.e. overweight/obesity (BMI  $\geq 25.0$ ; PAR% = 18.7%), heavy drinking ( $>196$  g/week (male) or  $>98$  g/week (female) of pure alcohol; PAR% = 15.4%), and aging ( $\geq 60$  years old; PAR% = 5.74%), although sex difference has the strongest effect (male; PAR% = 91.7%). A regression analysis revealed that all of these risks significantly increase SUA level, and that ABCG2 dysfunction had a stronger effect than other factors; a 25% decrease in ABCG2 function was equivalent to “an increase of BMI by 1.97-point” or “552.1 g/week alcohol intake as pure ethanol” in terms of ability to increase SUA. [Conclusion] ABCG2 dysfunction originating from common genetic variants revealed to have a stronger impact on the progression of hyperuricemia than other familiar risk factors. Our study will provide a better understanding of common genetic factors for common diseases including gout and hyperuricemia.

## ICW-B2-7

### Identification of the risk HLA variants of Graves' disease by applying the HLA imputation method to large scale Japanese genome-wide association study data

Yukinori Okada<sup>1,2</sup>

<sup>1</sup>Department of Human Genetics and Disease Diversity, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, <sup>2</sup>Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan

Conflict of interest: None

[Objectives] Graves' disease (GD) risk is strongly associated with genetic variations within the major histocompatibility complex (MHC) region, in particular to the human leukocyte antigen (HLA) variants.

However, its fine genetic architecture has not been elucidated. [Methods] To fine-map GD risk alleles within the MHC region in Japanese, we newly constructed a population-specific HLA reference panel consisting of the healthy subjects of Japanese ancestry ( $n = 908$ ). We conducted trans-ethnic comparisons of linkage disequilibrium (LD) and haplotype structures of the HLA variants by introducing a novel framework that utilizes an entropy-based LD measurement and a visualization tool capturing high-dimensional variables. Finally, we applied our HLA imputation method to the large-scale Japanese GD genome-wide association study (GWAS) data ( $n > 9,000$ ). [Results] The Japanese population demonstrated stronger LD between the HLA genes compared to European or other east Asian populations, highlighted by one population-specific common long-range HLA haplotype spanning through the entire MHC region from *HLA-A* to *HLA-DPB1* genes (haplotype frequency  $> 0.08$ ). Application of the HLA imputation method to the Japanese GD GWAS data and stepwise conditional analysis identified that amino acid polymorphisms of the multiple class I and class II HLA genes independently contribute to GD risk (HLA-DP $\beta$ 1 amino acid positions 35 and 9, HLA-A amino acid position 9, HLA-B amino acid position 45, and HLA-DR $\beta$ 1 amino acid position 74;  $P < 6.0 \times 10^{-7}$ ), with the strongest impact at *HLA-DPB1* ( $P < 1.0 \times 10^{-40}$ ). [Conclusion] Our study clearly and initially illustrates the value of the population-specific HLA reference panel for fine-mapping autoimmune disease risk within the MHC region for the Japanese population. Further application of the HLA imputation method to additional Japanese autoimmune disease GWAS data should be warranted.

## ICW-B3-1

### Three Cytokine Subsets Identified in Synovial Fluid from Rheumatoid Arthritis Patients Correlated with Clinical Parameters and Distinguishable from Other Inflammatory Arthropathies

Yasushi Kondo<sup>1</sup>, Katsuya Suzuki<sup>1</sup>, Masaru Takeshita<sup>1</sup>, Yoshiaki Kasai<sup>2</sup>, Takahiro Miyazaki<sup>2</sup>, Rinpei Morita<sup>3</sup>, Yasuo Niki<sup>4</sup>, Hiroshi Inoue<sup>5</sup>, Takeo Sakurai<sup>5</sup>, Noriyuki Seta<sup>1,6</sup>, Hironari Hanaoka<sup>1</sup>, Yuko Kaneko<sup>1</sup>, Hidekata Yasuoka<sup>1</sup>, Kunihiro Yamaoka<sup>1</sup>, Tsutomu Takeuchi<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, <sup>2</sup>Inflammation Drug Discovery Unit, Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited, Japan, <sup>3</sup>Department of Microbiology and Immunology, Keio University School of Medicine, Tokyo, Japan, <sup>4</sup>Department of Orthopedic Surgery, Keio University School of Medicine, Japan, <sup>5</sup>Inoue Hospital, Japan, <sup>6</sup>Internal Medicine, Tokyo Dental College Ichikawa General Hospital, Japan

Conflict of interest: Yes

[Objectives] We performed the comprehensive analysis of SF cytokines to clarify the relationships between synovial fluid (SF) cytokine profile and clinical information in rheumatoid arthritis (RA) and to differentiate from other inflammatory arthropathies. [Methods] In this cross-sectional, multicenter study, we enrolled 49 arthritis patients and divided them into 3 disease subgroups as 28 RA, 14 osteoarthritis (OA) and 7 other arthritis including spondyloarthritis and crystal induced arthritis. SF samples were obtained by arthrocentesis or at the time of joint replacement. Twenty cytokines, granzyme A and B by were measured and clustering analysis based on correlation coefficient among SF cytokines in each subgroup were analyzed. Correlation with cytokines and clinical parameters were also examined in RA patients [Results] Median age, disease duration and DAS28-ESR were 60 years old, 4.5 years and 5.36 in RA, respectively. Correlation and concentration of each cytokines were distinguishable from each disease group. Within RA group, we identified 3 distinctive cytokine subsets linking to the clinical parameters. The 1<sup>st</sup> subset contains IL-6, IL-8 and VEGF, which strongly correlated with local joint inflammation marker including CRP, SF cell count and ultrasound findings. The 2<sup>nd</sup> subset contains IL-1 $\beta$ , IL-10 and granzyme A, which correlated with not only local inflammation but also systemic disease activities. The 3<sup>rd</sup> subset including fractalkine, granzyme B, IL-17A did not show obvious relationships with any clinical parameter but this unique cluster was only seen in RA patients. [Conclusion] We found 3 characteristic cytokine clusters in SF that correlated with clinical parameters in RA patients, which were distinguishable from other inflammatory arthropathies.



## ICW-B3-2

### IL-38: A New Factor in Rheumatoid Arthritis

Shinjiro Kaieda<sup>1</sup>, Masaki Okamoto<sup>1</sup>, Masaki Tominaga<sup>1</sup>, Naomi Yoshida<sup>1</sup>, Yukiko Kunitake<sup>1</sup>, Daisuke Wakasugi<sup>1</sup>, Katsuya Kanasaki<sup>2</sup>, Hiroaki Ida<sup>1</sup>

<sup>1</sup>Department of Medicine 1, Division of Respiratory, Neurology and Rheumatology, Kurume University School of Medicine, Japan, <sup>2</sup>Nagata Orthopedic Hospital, Japan

Conflict of interest: None

[Objectives] IL-38 (IL-1F10) was originally described as an IL-1 family cytokine, and named IL-1HY2. IL-38 shares 37% homology with IL-1 receptor antagonist (IL-1Ra), 43% homology with IL-36 receptor antagonist, and has a three-dimensional structure similar to IL-1Ra. IL-38 was recently shown to inhibit *Candida albicans*-induced IL-17 production by human memory T cells. However, the role of IL-38 in inflammatory diseases such as rheumatoid arthritis (RA) remains unclear. [Methods] We isolated recombinant human IL-38 protein using the full length of human IL-38 cDNA. We established anti-human IL-38 monoclonal antibodies to perform immunohistochemical staining and enzyme-linked immunosorbent assay (ELISA). The serum levels of IL-38 in 137 RA and 26 OA patients, and in 56 healthy donors, were determined by ELISA. Synovial tissue was derived from knee joints of patients with 7 RA and 2 osteoarthritis (OA) patients. Arthritis was initiated in mice lacking IL-38, as well as their wild-type littermates, via intraperitoneal administration of K/BxN mouse serum. Total RNA was isolated from mouse ankle joints and IL-1 $\beta$  and IL-6 mRNA were quantified by qRT-PCR. [Results] The serum levels of IL-38 were  $5.7 \pm 0.4$  ng/mL,  $2.8 \pm 0.8$  ng/mL, and  $2.8 \pm 0.7$  ng/mL in RA patients, OA patients, and healthy donors, respectively. Further, IL-38 protein was highly expressed in the synovial lining of RA synovium. Moreover, we found that IL-38-deficient mice exhibited significant exacerbation of their arthritis clinical scores, compared with wild-type littermates. Correspondingly, histological measures of arthritis were also exacerbated, and accompanied by higher IL-1 $\beta$  and IL-6 gene expression in the ankle joints than seen in control mouse. [Conclusion] Our present study is the first to identify the presence of soluble IL-38 protein in the serum and its expression in the synovium of RA patients. IL-38 may play a role as an inhibitor in the pathogenesis of RA.

## ICW-B3-3

### TIARP suppresses the migration of neutrophils via the inhibition of CXCL2/CXCR2 expression

Asuka Inoue<sup>1</sup>, Isao Matsumoto<sup>1</sup>, Naoto Umeda<sup>1</sup>, Yuki Tanaka<sup>1</sup>, Yuko Kurashima<sup>1</sup>, Hoshimi Kawaguchi<sup>1</sup>, Hiroshi Ebe<sup>1</sup>, Satoru Takahashi<sup>2</sup>, Takayuki Sumida<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan, <sup>2</sup>Department of Anatomy and Embryology, University of Tsukuba, Ibaraki, Japan

Conflict of interest: None

**Objective** TIARP is dominantly expressed in macrophages (M $\phi$ ), neutrophils (Neu) and fibroblast-like synoviocytes (FLS). Recently, we found that TIARP functions as a negative regulator in autoimmune arthritis through the suppression of IL-6 production, NF- $\kappa$ B, STAT3 signaling in M $\phi$ , although the molecular mechanism of TIARP-expressing cells in arthritis remains uncertain. The purpose of this study is to elucidate functional role of TIARP in the pathogenesis of arthritis, especially focusing on Neu and FLS. **Methods** 1) RNAs were extracted from TIARP<sup>-/-</sup> or WT Neu, and subsequently compared by Gene chip. 2) The expression of CXCR1/2 on Neu was analyzed by qPCR. 3) The chemoattractant activity of WT or TIARP<sup>-/-</sup> Neu was tested by transwell chemotaxis assays. 4) Using WT or TIARP<sup>-/-</sup> FLS, the expression of IL-6, TNF $\alpha$  and CXCL2 after TNF $\alpha$  stimulation were detected. 5) To verify the effect of CXCL2 on the chemotactic activity, we performed the chemotaxis assay by applying to the lower chamber with anti-CXCL2 Ab or control IgG. 6) The production of IL-17 in the supernatant from Neu stimulated by immune-complex (IC) were measured by ELISA. **Results** 1) Gene ontology (GO) analysis of upregulated genes in TIARP<sup>-/-</sup> Neu demonstrated the enrichment of genes involved in immune response and chemotaxis. 2) The expression of CXCR1/2 was significantly higher in TIARP<sup>-/-</sup> Neu. 3) The recruitment was enhanced in TIARP<sup>-/-</sup> Neu compared to those in WT Neu. 4) The expressions of IL-6, TNF $\alpha$  and CXCL2 in TIARP<sup>-/-</sup> FLS

were significantly higher than in WT. 5) The numbers of migrated Neu were significantly decreased by the addition of anti CXCL2 Ab. 6) The production of IL-17 after IC-stimulation were not different between WT and TIARP<sup>-/-</sup> Neu. **Conclusion** TIARP might down-regulate the production of CXCL2 from FLS and the expression of CXCR1/2 in Neu, but not affect the production of IL-17, resulting in the protective ability of Neu migration in arthritic joints.

## ICW-B3-4

### CXCR4 Links the Shared Epitope to Anti-CCP Antibody Production in Rheumatoid Arthritis

Yasuo Nagafuchi, Hirofumi Shoda, Shuji Sumitomo, Shinichiro Nakachi, Rika Kato, Yumi Tsuchida, Haruka Tsuchiya, Keiichi Sakurai, Norio Hanata, Shoko Tateishi, Hiroko Kanda, Keishi Fujio, Kazuhiko Yamamoto  
Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Conflict of interest: None

[Objectives] Strong association between anti-CCP antibody and HLA-DRB1 allele carrying the shared epitope (SE) have been known in rheumatoid arthritis (RA). To explore the immunological effects of SE, RA patients were examined with immunophenotyping. A chemokine receptor CXCR4, known to play an important role in the CD4<sup>+</sup> T cell accumulation to the synovium, was also analyzed. [Methods] We performed flow cytometric immunophenotyping and HLA-DR quantitation of peripheral blood mononuclear cells (PBMC) CD4<sup>+</sup> T cells, B cells, NK cells, monocytes, and dendritic cells of 71 healthy donors (HD) and 82 RA patients. RA patients were also typed for HLA-DRB1. CXCR4 expressions of CD4<sup>+</sup> T cell subsets were also examined on 6 synovial fluids and 50 PBMC samples. [Results] PBMC Th1, Th17, Tfh and Treg subset ratios were decreased and showed no correlation to DAS28 in RA. CD45RA<sup>+</sup> Memory CD4<sup>+</sup> T cell ratios were increased in SE<sup>+</sup> RA patients and correlated to anti-CCP antibody levels. B cell and Monocyte HLA-DRB1 quantitation levels were increased only in SE<sup>+</sup> RA patients. CXCR4 was 92.6% positive on synovial CD4<sup>+</sup> T cells and increased on all PBMC CD4<sup>+</sup> T cell subsets in RA as compared to HD. PBMC memory CD4<sup>+</sup> T cells' CXCR4<sup>+</sup> ratio was positively correlated to B cell HLA-DRB1 quantitation level, DAS28, and anti-CCP antibody levels. [Conclusion] This study suggests that shared epitope is related to higher HLA-DRB1 expressions on B cells, which facilitate efficient antigen presentation and increase memory CD4<sup>+</sup> T cell ratio and higher CXCR4 expressions on memory CD4<sup>+</sup> T cells. It could be linked to CD4<sup>+</sup> T cell synovial migration and anti-CCP antibody production.

## ICW-B3-5

### Effect of Omega-3 Lipid Mediator Resolvin E1 on IL-1 $\beta$ induced IL-6 Production in Human Rheumatoid Synovial Fibroblasts

Yasuyuki Hasegawa, Miki Takada, Tomoya Harada, Ryota Okazaki, Akira Yamasaki, Eiji Shimizu

Department of Respiratory Medicine and Rheumatology, Faculty of Medicine, Tottori University, Yonago, Japan

Conflict of interest: None

[Objectives] Acetylsalicylic acid (ASA) irreversibly inhibits prostaglandin production, but may promote the production of specialized pro-resolving mediators derived from omega-3 polyunsaturated fatty acid ( $\omega$ -3 PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Resolvin E1 (RvE1; 5S, 12R, 18R-trihydroxyeicosapentaenoic acid) is one of the potent pro-resolving lipid mediator derived from EPA. We investigated the effect of RvE1 on IL-1 $\beta$  induced IL-6 production in RA synovial fibroblasts (RASf). [Methods] Human primary RASf were obtained at the time of joint replacement surgery. RASf were cultured with PUFAs for 72 hours. PUFAs treated cells were treated with ASA or RvE1, followed by IL-1 $\beta$  stimulation. IL-6 production in supernatant were measured by ELISA. COX2 and mPGES1 m-RNA and protein expression were analyzed by real-time PCR and western blotting. IL-6 mRNA was also determined by real time PCR. We examined the expression of ChemR23, phosphorylated ERK, AKT and I $\kappa$ B- $\alpha$  in RASf treated with RvE1 by western blotting. [Results] IL-1 $\beta$  induced IL-6 production in supernatant and mRNA expression were significantly re-

duced by EPA and DHA treatment with or without ASA compared to vehicle control. EPA and DHA treatment alone did not statistically reduce either COX2 or mPGES1 protein expression. However, ASA treatment in addition to EPA and DHA significantly reduced IL-1 $\beta$  induced mPGES1 protein expression. RvE1 significantly inhibits IL-1 $\beta$  induced IL-6 production, and also increased ChemR23 expression in RASF. RvE1 increased phosphorylation of AKT and decreased phosphorylation of I $\kappa$ B- $\alpha$  in RASF stimulated with IL-1 $\beta$ . On the other hand, inhibition of AKT signaling with wortmannin increased IL-1 $\beta$  induced mPGES1, COX2 and IL-6 mRNA production treated with RvE1. [Conclusion] IL-6 and mPGES1 production were synergistically reduced by treatment with EPA and DHA in addition to ASA. RvE1 inhibits IL-1 $\beta$  induced IL-6 production in RASF via ChemR23 and AKT pathway.

### ICW-B3-6

#### Regulation of humoral immune responses by TGF- $\beta$ -producing CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup> regulatory T cells

Tomohisa Okamura<sup>1,2</sup>, Kaoru Morita<sup>1</sup>, Yukiko Iwasaki<sup>1</sup>, Mariko Inoue<sup>1</sup>, Toshihiko Komai<sup>1</sup>, Shuji Sumitomo<sup>1</sup>, Shinichiro Nakachi<sup>1</sup>, Hirofumi Shoda<sup>1</sup>, Keishi Fujio<sup>1</sup>, Kazuhiko Yamamoto<sup>1</sup>

<sup>1</sup>Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, <sup>2</sup>The University of Tokyo Max Planck-The University of Tokyo Center for Integrative Inflammolgy, Tokyo, Japan

Conflict of interest: Yes

**[Objectives]** Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by autoantibody production. Early growth response gene-2 (*EGR2*) gene, a zinc-finger transcription factor, is known to affect susceptibility to SLE in human. We previously reported CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup>LAG3<sup>+</sup> regulatory T cells (LAG3<sup>+</sup> Tregs) that characteristically express *Egr2*. Therefore, we have examined whether LAG3<sup>+</sup> Tregs control humoral immunity. **[Methods]** C57BL/6 (B6) B cells and OT-II helper T (Th) cells were injected into Rag1KO mice in combination with LAG3<sup>+</sup> Tregs from B6, *Egr2* conditional knockout (CKO) (*Egr2<sup>fl/fl</sup>*CD4-*Cre*<sup>+</sup>), or *Fas*-mutated *B6<sup>lpr</sup>* mice. Mice were subsequently immunized with NP-OVA/alum twice. To examine the therapeutic effects in lupus-prone mice, MRL/*lpr* mice were injected with LAG3<sup>+</sup> Treg from MRL/+ mice. **[Results]** In Rag1KO mice transferred with B cells and OT-II Th cells, only transfer of B6 LAG3<sup>+</sup> Tregs significantly suppressed NP-specific antibody responses and the development of germinal center B cells (GCB) and follicular helper T cells (T<sub>FH</sub>). Interestingly, LAG3<sup>+</sup> Tregs produced high amounts of TGF- $\beta$ 3 in an *Egr2*- and *Fas*-dependent manner. TGF- $\beta$ 3 markedly suppressed B cell proliferation, strongly induced B cell death, and suppressed IgG production. The addition of TGF- $\beta$ 3 significantly reduced the phosphorylation of STAT6, Syk, and NF- $\kappa$ B p65 in activated B cells. As expected, treatment with an anti-TGF- $\beta$ 3 or anti-FasL blocking antibody cancelled the suppressive activity of LAG3<sup>+</sup> Treg in the Rag1KO mice. In lupus-prone mice, MRL/+ LAG3<sup>+</sup> Tregs, but not CD4<sup>+</sup>CD25<sup>+</sup> Tregs, also significantly suppressed the progression of nephritis and autoantibody production in MRL/*lpr* mice in a TGF- $\beta$ 3-dependent manner. **[Conclusion]** These results clarified the molecular basis underlying LAG3<sup>+</sup> Treg-mediated B cell regulation, which indicated that TGF- $\beta$ 3-producing LAG3<sup>+</sup> Tregs may be a suitable therapeutic target for autoantibody-mediated autoimmune diseases, including SLE.

### ICW-B4-1

#### Loss of SH3BP2 function suppresses bone destruction in TNF-driven and collagen-induced arthritis mouse models

Tomoyuki Mukai<sup>1,2</sup>, Keiichiro Nishida<sup>3,4</sup>, Yoshitaka Morita<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Kawasaki Medical School, Kurashiki, Japan, <sup>2</sup>Department of Oral and Craniofacial Sciences, School of Dentistry, University of Missouri-Kansas City, Kansas City, USA, <sup>3</sup>Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, <sup>4</sup>Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Conflict of interest: None

[Objectives] SH3BP2 is a signaling adapter protein which regulates

immune and skeletal systems. The purpose of this study was to investigate the role of SH3BP2 in arthritis in human TNF transgenic (hTNFtg) and collagen-induced arthritis (CIA) models. [Methods] First, SH3BP2-deficient (Sh3bp2<sup>-/-</sup>) and wild-type (Sh3bp2<sup>+/+</sup>) mice were crossed with hTNFtg mice. Inflammation and bone loss were examined by clinical inspection and histological and micro-CT analyses. Osteoclastogenesis was evaluated with primary bone marrow-derived M-CSF-dependent macrophages (BMMs). Second, CIA was induced in Sh3bp2<sup>-/-</sup> and Sh3bp2<sup>+/+</sup> mice, and the incidence and severity of arthritis were evaluated. Anti-mouse type II collagen (CII) antibody levels were measured by ELISA. Lymph node cell responses to CII were also determined. [Results] SH3BP2-deficiency did not alter the severity of joint swelling but suppressed bone erosion in the hTNFtg model. Bone loss of talus and tibia was prevented in Sh3bp2<sup>-/-</sup>/hTNFtg mice compared to Sh3bp2<sup>+/+</sup>/hTNFtg mice. RANKL- and TNF-induced osteoclastogenesis was suppressed in Sh3bp2<sup>-/-</sup> BMM cultures. NFATc1 nuclear localization in response to TNF was decreased in Sh3bp2<sup>-/-</sup> BMMs compared to Sh3bp2<sup>+/+</sup> BMMs. In the CIA model, SH3BP2-deficiency suppressed the incidence of arthritis, which was associated with decreased anti-CII antibody production, while the antigen-specific T-cell responses in lymph nodes were not significantly different between Sh3bp2<sup>+/+</sup> and Sh3bp2<sup>-/-</sup> mice. [Conclusion] SH3BP2-deficiency prevents bone loss via impaired osteoclastogenesis in the hTNFtg model and suppresses the induction of arthritis via decreased autoantibody production in the CIA model. Therefore, SH3BP2 could be a therapeutic target for rheumatoid arthritis.

### ICW-B4-2

#### Contribution of semaphorin 4D (Sema4D) in rheumatoid arthritis (RA): increased soluble Sema4D enhanced RA inflammation and Sema4D antibody inhibited mouse collagen induced arthritis

Yuji Yoshida<sup>1</sup>, Atsushi Ogata<sup>1</sup>, Kosuke Ebina<sup>2</sup>, Kenrin Shi<sup>2</sup>, Toru Hirano<sup>1</sup>, Yoshihito Shima<sup>1</sup>, Masashi Narazaki<sup>1</sup>, Toshio Tanaka<sup>3</sup>, Hideki Tsuboi<sup>4</sup>, Yukihiko Saeki<sup>5</sup>, Tetsuya Tomita<sup>2,6</sup>, Atsushi Kumanogoh<sup>1</sup>

<sup>1</sup>Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Graduate School of Medicine, Osaka, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Osaka University Graduate School of Medicine, Osaka, Japan, <sup>3</sup>Department of Clinical Application of Biologics, Osaka University Graduate School of Medicine, Osaka, Japan, <sup>4</sup>Department of Rheumatology, National Hospital Organization Osaka Minami Medical Center, Kawachinagano, Japan, <sup>5</sup>Department of Clinical Research, National Hospital Organization Osaka Minami Medical Center, Kawachinagano, Japan, <sup>6</sup>Department of Orthopaedic Biomaterial Science, Osaka University Graduate School of Medicine, Osaka, Japan

Conflict of interest: Yes

**Objective.** Semaphorin 4D (Sema4D)/CD100 plays pleiotropic roles in immune activation, angiogenesis, bone metabolism, and neural development. In this study, we investigated the role of Sema4D in rheumatoid arthritis (RA). **Methods.** Soluble Sema4D (sSema4D) in the RA sera and synovial fluid were analysed by ELISA. Cell surface expression and transcript of Sema4D was analysed in RA peripheral blood cells. Immunohistochemical staining of Sema4D was performed in RA and OA synovium. The generation of sSema4D was evaluated in ADAMTS4 treated Sema4D expressing cell line THP-1. The efficacy of anti-Sema4D antibody was evaluated in mouse collagen-induced arthritis (CIA). **Results.** The serum and synovial fluid levels of sSema4D were elevated in RA patients. The serum Sema4D levels were correlated with RA disease activity markers. Although Sema4D expressing cells were accumulated in RA synovium, the cell surface expression of Sema4D on CD3<sup>+</sup> and CD14<sup>+</sup> cells were down regulated in RA. The transcripts of Sema4D were not changed. ADAMTS4, which increased in RA cleaved cell surface Sema4D and generate sSema4D. Additionally sSema4D induced IL-6 and TNF- $\alpha$  in CD14<sup>+</sup> monocytes, and IL-6 and TNF- $\alpha$  stimulated on ADAMTS4 production from synovial cells. It suggests that sSema4D/TNF- $\alpha$  and IL-6/ADAMTS4 axis functions as a vicious cycle, triggering an inflammatory loop that contributes to the pathogenesis of RA. Inhibited of CIA by anti-Sema4D antibody suggested that the blocking this vicious cycle by intercepting Sema4D signal may be useful for RA treatment. **Conclusion.** Sema4D might be important in vicious cycle of inflammation and Sema4D targeted therapy for RA is promising.

### ICW-B4-3

#### Grape seed proanthocyanidin extract ameliorates murine autoimmune arthritis via suppression of toll-like receptor 4-signaling pathways

Ji-Min Kim<sup>1</sup>, Jihye Bang<sup>2</sup>, Hyo-Jung Lee<sup>3</sup>, Tae-Han Lee<sup>1</sup>, Sang-Hyon Kim<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Dongsan Hospital, Keimyung University School of Medicine, Daegu, Korea, <sup>2</sup>Keimyung University School of Medicine, Daegu, Korea, <sup>3</sup>Department of Microbiology, Keimyung University School of Medicine, Daegu, Korea

Conflict of interest: None

[Objectives] Grape seed proanthocyanidin extract (GSPE), a natural plant constituent derived from grape seeds, has been reported to have diverse biologic properties. Although GSPE has been shown to have a beneficial effect on regulating inflammation, anti-inflammatory mechanism of GSPE still remains unclear. The aim of this study is to verify the influence of GSPE on toll-like receptor 4 (TLR4)-mediated signaling pathway, which plays a critical role in the development of autoimmune diseases such as rheumatoid arthritis (RA). [Methods] The experimental groups included saline-treated type II collagen-induced arthritis (CIA) group and GSPE-treated CIA group. The severity of arthritis was assessed clinically, biochemically and histologically. Immunostaining for TLR4 was performed. The expression of TLR4 and downstream signaling molecules was analyzed by western blot. The effect of GSPE on lipopolysaccharide (LPS)-induced TLR4 activation was also evaluated. [Results] GSPE attenuated the clinical severity of arthritis and reduced histological damage. GSPE decreased TLR4-stained cells in the synovium of CIA mice. Serum levels of tumor necrosis factor- $\alpha$ , interleukin (IL)-6 and IL-17 in GSPE-treated CIA mice were lower than those in saline-treated CIA mice. GSPE downregulated the expression of TLR4, myeloid differentiation factor 88 (MyD88), Toll-IL 1 receptor domain-containing adapter inducing interferon- $\beta$  and phosphorylated I $\kappa$ B $\alpha$  protein in the synovium of CIA mice. At the same time, GSPE inhibited nuclear translocation of nuclear transcription factor- $\kappa$ B (NF- $\kappa$ B) subunits p50 and p65. LPS-induced TLR4 activation was suppressed by GSPE in human fibroblast-like synoviocytes as well as in murine macrophages *in vitro*. [Conclusion] Our findings suggested that GSPE ameliorated CIA by regulating TLR4-MyD88-NF- $\kappa$ B signaling pathway. GSPE may serve as a possible therapeutic agent for treating immunologic diseases including RA, in the pathogenesis of which TLR4 activation is involved.

### ICW-B4-4

#### GCSB-5 attenuates murine autoimmune arthritis by suppressing Th17 cell differentiation

Sang-Hyon Kim<sup>1</sup>, Hyo-Jung Lee<sup>2</sup>, Jihye Bang<sup>3</sup>, Tae-Han Lee<sup>1</sup>, Ji-Min Kim<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Dongsan Hospital, Keimyung University School of Medicine, Daegu, Korea, <sup>2</sup>Department of Microbiology, Keimyung University School of Medicine, Daegu, Korea, <sup>3</sup>Keimyung University School of Medicine, Daegu, Korea

Conflict of interest: None

[Objectives] GCSB-5 is a purified extract from 6 crude herbs which have been used for treatment of several bone diseases in eastern Asia traditionally. This study was undertaken to demonstrate the anti-inflammatory effects of GCSB-5 in the collagen-induced arthritis (CIA) murine model and to investigate the action mechanism of GCSB-5. [Methods] CIA mice were treated with intragastric administration of GCSB-5 (0, 300, 600 mg/kg) or saline. Clinical and radiographical analyses were performed. Flow cytometry was used to determine Th17 cell population in spleens from GCSB-5-treated and untreated CIA mice. The effect of GCSB-5 on Th17 cell differentiation under a Th17-polarizing condition was also investigated *in vitro*. Western blot analysis was used for evaluating the influence of GCSB-5 on intracellular signaling of splenocytes. [Results] Both clinical arthritis and radiographical scores were decreased with the treatment of GCSB-5. Administration of GCSB-5 reduced the number of CD4+IL17+ T cells in the splenocytes of CIA mice. Under the Th17-inducing condition, GCSB-5 downregulated the differentiation of CD4+ T cells into Th17 cells *in vitro*. GCSB-5 also suppressed STAT3

phosphorylation at tyrosine705 and serine727 in a dose-dependent manner. [Conclusion] Our results suggest that GCSB-5 possesses an anti-inflammatory effect on murine autoimmune arthritis by inhibiting Th17 cell differentiation. GCSB-5 may be beneficial for the management of inflammatory diseases such as rheumatoid arthritis.

### ICW-B4-5

#### The anergy induction of M3R reactive CD4+ T cells suppresses experimental sialadenitis like Sjögren's syndrome *in vivo*

Hiromitsu Asashima, Hiroto Tsuboi, Hiroyuki Takahashi, Tomoya Hirota, Mana Iizuka, Yuya Kondo, Isao Matsumoto, Takayuki Sumida  
Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

Conflict of interest: None

[Objectives] Rag1<sup>-/-</sup> mice transferred with splenocytes of M3 muscarinic acetylcholine receptor (M3R)<sup>-/-</sup> mice immunized with M3R peptides mixture (N-terminal regions; N1, N2, N3, and extracellular loops; 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>) developed sialadenitis like Sjögren's syndrome (M3R induced sialadenitis; MIS). M3R reactive CD4+ T cells were indispensable, whose epitopes were both N1 and 1<sup>st</sup> regions. Altered peptide ligands (APLs), substituted in amino acid residues at TCR contact sites, can regulate the T cell activation. The study was designed to establish the antigen specific therapy and to clarify its mechanism. [Methods] 1) APLs of N1 and 1<sup>st</sup> peptide were synthesized and antagonistic APLs were selected by *in vitro* pre-pulse assay. 2) Antagonistic APLs were administered to MIS ([APLs]) on day 7 and 10 after the cell transfer. 3) Immunologically-relevant molecules of CD4+ T cells at the cervical lymph nodes were evaluated by PCR. Also the proliferative ability was evaluated. 4) The molecules related to the anergy were assessed by *in vitro* co-culture assay. [Results] 1) Seven N1 APLs (N1-APL 1-7) and eight 1<sup>st</sup> APLs (1<sup>st</sup>-APL 1-8) were designed, and of those, N1-APL5 (AA15 N $\rightarrow$ T), 6 (AA15 N $\rightarrow$ C) and 7 (AA15 N $\rightarrow$ S) significantly suppressed IFN $\gamma$  (p<0.05). 1<sup>st</sup>-APL8 (AA140 A $\rightarrow$ M) significantly suppressed IL-17 (p<0.05). 2) N1-APL7 significantly suppressed sialadenitis *in vivo* (p<0.05). 3) Egr-2, a transcription factor that regulates the anergic state, was significantly higher in the CD4+ T cells of [N1-APL7] than control. The cell proliferation was reversed by exogenous IL-2 administration in [N1-APL7]. 4) Egr-2 was significantly higher in the CD4+ T cells when cultured with N1-APL7, and also the downstream anergy related E3 ubiquitin ligases such as Itch, Cbl-b, and GRAIL, were significantly higher. [Conclusion] N1-APL7, selected as one of the antagonistic APLs *in vitro*, significantly suppressed the induction of MIS *in vivo*, possibly via the induction of anergic state of M3R reactive CD4+ T cells.

### ICW-B4-6

#### Semi-Automatic Computer-Based Roentgenographic Quantification of Joint Space Width Difference Using Temporal Subtraction-Initial Study with Joint Phantom and Metacarpo-phalangeal in Patients with Rheumatoid Arthritis

Tamotsu Kamishima<sup>1</sup>, Kou Katayama<sup>2</sup>

<sup>1</sup>Faculty of Health Science, Hokkaido University, Sapporo, Japan, <sup>2</sup>Katayama Orthopedic Rheumatology Clinic, Asahikawa, Japan

Conflict of interest: None

[Objectives] Radiograph is currently the gold standard for detection and follow-up of bone damage in rheumatoid arthritis (RA) in clinical practice. However, the disadvantages of this method include its low sensitivity for detecting slight changes in joint space narrowing (JSN) and disagreements between readers. Therefore, we developed and validated a computer-based quantification of joint space width difference using temporal subtraction which can detect slight JSN changes between two images and display the joint space difference index (JSDI). [Methods] In a phantom study, joint spaces from 0 mm to 5 mm (0.5 mm interval) were made between two phantom bones using the vacuum-sintered body of titanium medical apatite (TMA®). The difference in joint spaces was analyzed. We then applied this and the van der Heijde modified Sharp score to 257 metacarpophalangeal (MCP) joints in 27 rheumatoid patients, on treated with Tocilizumab to confirm that the JSDI reflects interval change in joint space. [Results] Positive correlation was found between the dif-

ference in joint spaces and the JSDI in TMA phantom study. There was no statistically significant difference in JSDI between left and right MCP joints ( $p = 0.791$ ). JSDI of the RA patients was significantly different between joints with and without JSN progression ( $p < 0.001$ ). [Conclusion] The computer-based quantification of joint space width difference using temporal subtraction can recognize the interval difference in MCP joint space on radiographs and quantifies its degree objectively.

#### ICW-B4-7

##### **Power Doppler signal calibration between ultrasound machines using a capillary flow phantom for pannus vascularity and rheumatoid finger joints -a preliminary study**

Tamotsu Kamishima<sup>1</sup>, Atsushi Noguchi<sup>2</sup>, Michihito Kono<sup>3</sup>, Tatsuya Atsumi<sup>2</sup>

<sup>1</sup>Faculty of Health Science, Hokkaido University, Sapporo, Japan, <sup>2</sup>Internal Medicine II, Hokkaido University Hospital, Japan, <sup>3</sup>Obihiro-Kosei General Hospital, Japan

Conflict of interest: None

[Objectives] Ultrasound allows detection and grading of inflammation in rheumatology. Despite these advantages of ultrasound in the management of rheumatoid patients, it is well known there are significant machine to machine disagreements for signal quantification as well as those between examiners. In this study, we tried to calibrate power Doppler (PD) signal of two models of ultrasound machine using a capillary flow phantom and MP joints of rheumatoid patients. [Methods] After flow velocity analysis in the perfusion cartridge in various injection rates, we measured signal count in the perfusion cartridge at various injection rates and PRFs (pulse repetition frequency) using PD. The perfusion cartridge was connected to an angiography injector, and a blood mimicking fluid was injected. Using the data from two models of ultrasound machine, LOGIQ E9 (GE) and AVIUS (HITACHI Aloka), the quantitative PD (QPD) index (the summation of the colored pixels in  $1\text{cm} \times 1\text{cm}$  rectangular ROI) was calculated via Image J (internet free software). Similarly, 2<sup>nd</sup> or 3<sup>rd</sup> metacarpophalangeal joints of 3 rheumatoid patients were assessed. [Results] In phantom study, we found negative correlations between PRF and QPD index when flow velocity was constant, and positive correlations between flow velocity and QPD index at constant PRF for both machine systems. In clinical study, we found negative correlations between PRF and QPD index when flow velocity was constant. [Conclusion] It was suggested that signal calibration of various models of ultrasound machine may be possible by adjusting the PRF setting.

#### ICW-B5-1

##### **Unc-51-like kinase 1 (ULK1) controls autophagy and maintains the balance between catabolic and anabolic factors in the articular cartilage**

Mira Abou Rjeili<sup>1</sup>, Yue Zhang<sup>1</sup>, Ying-hua Li<sup>1</sup>, Meryem Blati<sup>2</sup>, Jean-Pierre Pelletier<sup>2</sup>, Johanne Martel-Pelletier<sup>2</sup>, K. Wayne Marshall<sup>1</sup>, Nizar N. Mahomed<sup>1</sup>, Rajiv Gandhi<sup>1</sup>, Mohit Kapoor<sup>1</sup>

<sup>1</sup>Division of Genetics and Development, Toronto Western Research Institute, University Health Network, Toronto, Canada, <sup>2</sup>Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, Canada

Conflict of interest: None

**Objectives:** Autophagy is an essential, homeostatic process required for survival, differentiation, development and homeostasis. Our studies showed that genetic deficiency of mTOR upregulates autophagy and protects mice from OA. This study also identified that loss of mTOR in the articular cartilage resulted in increased expression of Unc-51-like kinase 1 (ULK1), the most upstream autophagy inducer. We hypothesized that ULK1 is required for the induction of autophagy in the articular cartilage and maintain the balance between catabolic and anabolic factors implicated in OA pathophysiology. **Methods and Results:** Our studies show that in human OA cartilage (compared to normal human cartilage) and mouse experimental OA cartilage (compared to sham-control cartilage), expression of ULK1 is significantly down-regulated in OA condition. This loss of ULK1 expression correlates with increased rate of chondrocyte apoptosis during OA. Since rapamycin (mTOR complex 1 inhibitor)

up-regulates autophagy; we pre-treated OA chondrocytes with rapamycin and transfected these cells in the presence/absence of ULK1 siRNA to determine if silencing of ULK1 can reverse the protective effects of rapamycin. Indeed, silencing of ULK1 in rapamycin-treated OA chondrocytes resulted in a significant decrease in the expression of LC3B (required for autophagosome formation) as well as mRNA expression of LC3 and ATG5. Furthermore, silencing of ULK1 in rapamycin-treated OA chondrocytes resulted in a significant increase in the expression of OA catabolic factors (MMP-13 and CCL2). **Conclusion:** These results suggest that in the articular cartilage, ULK1 is essential for induction of autophagy and may in part be responsible for maintaining the balance between catabolic and anabolic processes. To further investigate the exact in vivo role of ULK1 in articular cartilage homeostasis, we are now generating cartilage-specific ULK1 knockout mice using LoxP/Cre system and subject these mice to OA surgery.

#### ICW-B5-2

##### **Differential regulation of autophagy in articular cartilage chondrocytes and synovial fibroblasts during Osteoarthritis**

Alexa Parousis, Yue Zhang, Mohit Kapoor  
University Health Network, Toronto Western Hospital, Toronto, Canada

Conflict of interest: Yes

Osteoarthritis (OA) is the most common form of arthritis. Two major joint structures that typically play a key role in the initiation and progression of OA include articular cartilage and synovium. During the patho-progression of OA, chondrocytes undergo accelerated cell death. Contrastingly, synovial fibroblasts exhibit the opposite proliferative and replication phenotype to chondrocytes. **Objective:** During OA, synovial fibroblasts tend to proliferate faster and exhibit higher rate of cell survival. Understanding the exact cellular survival mechanisms in chondrocytes and synovial fibroblasts within the joint structure is essential to devise strategies to achieve joint homeostasis. We have previously shown that process of autophagy, a cell survival mechanism, is significantly compromised in the articular chondrocytes during OA, we investigated the expression and regulation of autophagy markers in OA synovial fibroblasts. **Methods:** Human synovial tissue was harvested from patients undergoing knee replacement surgery. Synoviocytes were isolated from tissue using enzymatic digestion. Normal patient cells were derived post-mortem. Cells were treated with TGF- $\beta$  or vehicle. **Results:** We observed a significant up-regulation in the expression of critical autophagy activity markers including LC3B, ULK1, AMPK1, and ATG3 in synovial fibroblasts from OA patients compared to healthy controls. Further, we determined the expression of TGF- $\beta$ , major profibrotic factor was upregulated in OA. Compared to healthy control fibroblasts, OA fibroblasts exhibit increased expression of TGF- $\beta$ 1. **Conclusion:** Our results showed that synovial fibroblasts exhibit enhanced autophagy which that may contribute the hyperplastic phenotype seen in synovial tissue during OA. These results show that two joint structures (articular cartilage and synovium) exhibit differential autophagy regulation during OA. Autophagy may represent a potential therapeutic target in OA synovium.

#### ICW-B5-3

##### **Identification of synovial fluid microRNAs as potential OA biomarkers**

Ying-Hua Li<sup>1</sup>, Rajiv Gandhi<sup>2</sup>, Amanda Weston<sup>2</sup>, Daniel Antfleck<sup>2</sup>, Bahareh Saffar<sup>1</sup>, Rod Davey<sup>2</sup>, Khalid Syed<sup>2</sup>, Nizar N. Mahomed<sup>2</sup>, Mohit Kapoor<sup>1</sup>

<sup>1</sup>Toronto Western Research Institute, Division of Genetics and Development, Toronto Western Hospital, University Health Network, Toronto, Canada, <sup>2</sup>Division of Orthopedic Surgery, University Health Network, Toronto Western Hospital, Toronto, Canada

Conflict of interest: None

**[Objectives]** (1) To identify differentially expressed microRNAs (miRNAs) in synovial fluid from endstage OA patients undergoing total knee replacement surgery compared to early-stage OA patients undergoing arthroscopic surgery. (2) To explore the use of these differentially expressed miRNAs as potential OA biomarkers. **[Methods]** miRCURY LNA Universal RT microRNA PCR Human panel I+II arrays was used for profiling study and quantitative real-time PCR was used for valida-

tion. **[Results]** We recently performed a miRNA profiling of synovial fluid from 4 endstage and 4 early-stage OA patients using miRCURY LNA PCR arrays containing 752 miRNAs and identified 14 differentially expressed miRNAs in end stage OA compared to early-stage OA. Among these, expression of three miRNAs (miR-27a-3p, miR-378 and miR-101) was only detected in endstage OA, six miRNAs (miR-23a, miR-24, miR-29c, miR-34a, miR-186, miR-27b) were up-regulated and five miRNAs (miR-934, miR-329, miR-655, miR-27a-5p and miR-708-3p) were down-regulated. At second stage of this study, we validated the expression of these 14 miRNAs in 51 synovial fluid samples from 27 endstage OA patients and 24 early-stage OA patients respectively. Nine miRNAs (miR-23a, miR-24, miR-29c, miR-34a, miR-186, miR-27b, miR-27a-3p, miR-27a-5p and miR-378) remained to be significantly differentially expressed irrespective of gender. Importantly this is the first study to profile miRNA expression in synovial fluid and four miRNAs identified in our study have never been reported to be involved in OA. Our ongoing work will investigate if each of these identified miRNAs exhibits any pathophysiological role in OA. **[Conclusion]** We identified and validated seven miRNAs differentially expressed in synovial fluid in endstage OA patients compared to early-stage OA patients. These miRNAs have the potential to serve as minimally invasive OA biomarkers.

### ICW-B5-4

#### Up-regulation of CCL18-CCR8 signaling in patients with IgG4-related disease

Hiroto Tsuboi, Mana Iizuka, Hiromitsu Asashima, Hiroyuki Takahashi, Tomoya Hirota, Yuya Kondo, Isao Matsumoto, Takayuki Sumida  
Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

Conflict of interest: None

**[Objectives]** IgG4-related disease (IgG4-RD) is a new disease entity characterized by high serum IgG4 levels, infiltration of IgG4-positive plasmacytes and fibrosis in various organs. Recently we have clarified that Th2 and regulatory T cell (Treg) cytokines such as IL-10 and TGF $\beta$ , activation-induced cytidine deaminase (AID), and CCL18 were up-regulated in labial salivary glands (LSGs) of IgG4-RD compared with Sjögren's syndrome (SS) and healthy controls by quantitative PCR. These molecules might contribute to IgG4-class switch recombination and fibrosis in IgG4-RD. The purpose of this study is to clarify the expression of CCL18, CCR8 which has been identified as a receptor for CCL18, and expressing cells of these chemokine and chemokine receptor in IgG4-RD. **[Methods]** 1) The mRNA expression levels of CCL18 and CCR8 in peripheral blood mononuclear cells (PBMCs) were compared between IgG4-RD (N=4), SS (N=3), and controls (N=6) by quantitative PCR. 2) The expression of CCL18 on macrophages (CD68) and B cells (CD20) in LSGs were compared between IgG4-RD (N=2), SS (N=1), and control (N=1) by immunofluorescence (IF) staining. 3) The expression of CCR8 and expressing cells (CD3, CD20, and CD138) were examined by IF in lacrimal glands of IgG4-RD (N=1). **[Results]** 1) There was no significant difference in mRNA expression levels of CCL18 and CCR8 between PBMCs of IgG4-RD, SS, and controls (N.S). 2) The expression of CCL18 on CD68+macrophages and CD20+B cells was observed in LSGs of IgG4-RD, whereas not observed in LSGs of SS and control. 3) Many CD3+T cells, some CD138+plasmacytes, and a few CD20+B cells expressed CCR8 in lacrimal glands of IgG4-RD. **[Conclusion]** These findings suggested that CCL18-CCR8 signaling was up-regulated in affected tissues, whereas not in PBMCs, and this axis might contribute to the pathogenesis of IgG4-RD.

### ICW-B5-5

#### Low density granulocytes may be associated with interstitial lung disease in dermatomyositis: a potential contributor

Sigong Zhang<sup>1,2</sup>, Guochun Wang<sup>2</sup>

<sup>1</sup>Lanzhou University Second Hospital, Lanzhou, China, <sup>2</sup>China-Japan Friendship Hospital, Beijing, China

Conflict of interest: None

**[Objectives]** Abnormal regulation of Neutrophil extracellular traps (NETs) are potential contributor to interstitial lung disease (ILD) in der-

matomyositis (DM). Low density granulocytes (LDGs) exhibit an enhanced NETs formation ability. This study tests the hypothesis that LDGs are involved in pathogenesis of DM associated-ILD. **[Methods]** Forty eight DM patients (28 with ILD) and 19 healthy volunteers were recruited for this study. LDGs percentage in peripheral blood mononuclear cells (PBMCs) was tested by flow cytometer. Neutrophil-related genes (LL-37, MPO and MMP-8) expression in PBMCs were tested by quantitative RT-PCR. Myositis Disease Activity Assessment Visual Analogue Scales (MYOACT) was used to assess the disease activity. **[Results]** LDGs percentage in PBMCs was 7.1-fold higher in DM patients than healthy control. LDGs percentage in PBMCs was 2.7-fold higher in DM patients with ILD than DM patients without ILD. The mRNA expression level of LL-37, MPO and MMP-8 and LL-37 protein level in DM group were significant higher than those in Control group. LDGs percentage positively correlated with MYOACT lung disease activity scores. **[Conclusion]** LDGs percentage was significantly increased in DM patients with ILD and positively correlated with MYOACT lung disease activity scores, suggesting that abnormally increased LDGs are potential contributors to pathogenesis of DM-associated ILD.

### ICW-B5-6

#### Injury and subsequent regeneration of muscles activate local innate immunity to facilitate development and relapse of autoimmune myositis

Naoki Kimura, Hirata Shinya, Nobuyuki Miyasaka, Kimito Kawahata, Hitoshi Kohsaka

Department of Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), Tokyo, Japan

Conflict of interest: None

**[Objectives]** To discern if injury and subsequent regeneration of the skeletal muscles induce inflammatory milieu that can facilitate development and relapse of autoimmune myositis. **[Methods]** The quadriceps of C57BL/6 mice were injured with bupivacaine (BPVC) and evaluated histologically. After 3 days, macrophages in the treated muscles were collected and examined for cytokine expression with reverse transcriptase-polymerase chain reaction. Cytokine production by regenerating muscle fibers and differentiating C2C12 myotubes was evaluated with immunohistochemistry and enzyme-linked immunosorbent assay. Mice were immunized with C protein fragments at the tail bases and right hind footpads (day 0) to evoke systemic anti-C-protein immunity and to induce local myositis in the right hind limbs. The contralateral quadriceps were injured with BPVC or phosphate buffered saline (PBS) at day 7, or after spontaneous regression of myositis (day 42). The quadriceps from the unimmunized mice were injured with BPVC at day 7. The muscles were examined histologically 14 days after the treatments. **[Results]** The muscles had infiltration of macrophages most abundantly at 3 days after the BPVC injection with emergence of regenerating fibers from 5 days. The macrophages expressed inflammatory cytokines including TNF $\alpha$ , IL-1 $\beta$ , and CCL2. In vivo regenerating fibers and in vitro differentiating myotubes also expressed the inflammatory cytokines. The BPVC-injected muscles from the unimmunized mice had regenerating fibers with resolved inflammatory cell infiltration 14 days after the treatment. In contrast, when mice were preimmunized with the C protein fragments, the muscles injured with BPVC, but not with PBS, at day 7 as well as at day 42 accompanied myositis with CD8+ T cell infiltration. **[Conclusion]** Regenerating muscle fibers as well as macrophages might effectively contribute to set up inflammatory milieu in the muscles and facilitate development and relapse of autoimmune myositis.

### ICW-B5-7

#### CXCR5+Th2 and the dysregulation of B cell reactions contribute to IgG4 production in IgG4-related disease

Mitsuhiro Akiyama<sup>1</sup>, Katsuya Suzuki<sup>1</sup>, Hidekata Yasuoka<sup>1</sup>, Kunihiro Yamaoka<sup>1</sup>, Masaru Takeshita<sup>1</sup>, Yoshiaki Kassai<sup>2</sup>, Takahiro Miyazaki<sup>2</sup>, Rimpei Morita<sup>3</sup>, Yuko Kaneko<sup>1</sup>, Tsutomu Takeuchi<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, <sup>2</sup>Inflammation Drug Discovery Unit, Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited, Tokyo, Japan, <sup>3</sup>Department of Microbiology and Immunology, Keio University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] The significance of distinct T and B cell abnormalities in IgG4-related disease (IgG4-RD) remains to be established. We took this study to analyze the phenotype of circulating T and B cell subsets and serum cytokine levels and their association with IgG4 production in patients with active untreated IgG4-RD. [Methods] Peripheral T and B cells from 15 patients with active, untreated, biopsy-proven IgG4-RD, 19 patients with primary Sjögren's syndrome (SS) and 23 healthy controls (HC) were analyzed by multi-color flow cytometry. Multiple serum cytokines (IL-4, IL-5, IL-6, IL-10, IL-13, IL-21, IL-33 and IFN- $\gamma$ ) were analyzed using cytokine bead array and enzyme-linked immunosorbent assay. Relationship among proportion of circulating T and B cell subsets, serum cytokine levels and serum IgG4 concentrations were examined. [Results] IgG4-RD patients had substantially high proportion of CXCR5+Th2 cells compared to SS and HC. Increased proportion of CXCR5+Th2 cells and plasmablasts strongly correlated with serum IgG4 concentrations in IgG4-RD. Of serum cytokines, serum IL-4 levels correlated with serum IgG4 concentrations in addition to increased proportion of CXCR5+Th2 cells and plasmablasts. Moreover, increased proportion of CXCR5+Th2 cells correlated with increased proportion of plasmablasts in IgG4-RD but not SS and HC. [Conclusion] Our study suggests that CXCR5+Th2 and the dysregulation of B cell reactions may contribute to IgG4 production by the effect of IL-4 in patients with IgG4-RD.

### ICW-B6-1

#### The role of natural antibodies in acute cell death-induced inflammation

Hiroshi Kataoka<sup>1</sup>, Hajime Kono<sup>2</sup>

<sup>1</sup>Department of Rheumatology and Clinical Immunology, Sapporo City General Hospital, Sapporo, Japan, <sup>2</sup>Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] Damage associated molecular patterns (DAMPs) released from dying cells mediate dead cell-induced inflammation. However, little is known about whether host factors like immune components contribute to the inflammatory response. The aim of this study is to test whether natural antibodies have a role in acute cell death-induced inflammation in two different models, dead cell-induced peritonitis and acetaminophen-induced liver damage in C57BL/6 mice. [Methods] To see whether there is potential contribution of natural antibodies to cell death-induced inflammation, early (4h) and late (16h) neutrophilic responses to injured murine T lymphoma cell line, EL4 cells, injected into peritoneal cavity of C57BL/6 mice or of mice genetically lacking antibodies,  $\mu$ MT mice, were quantified by flow cytometry. Neutrophil infiltration into liver 16h after peritoneal administration of acetaminophen was compared between  $\mu$ MT mice and control C57BL/6 mice. Then acute inflammatory cell recruitment in injured cell-induced peritonitis and acetaminophen-induced liver damage was quantitated by flow cytometry in  $\mu$ MT mice and serum-transferred  $\mu$ MT mice. [Results] Peritoneal neutrophil and monocyte recruitment in early (4h) and late (16h) response to injured EL4 cells was markedly decreased in  $\mu$ MT mice. This was reversed to the wild-type level by serum transfer to  $\mu$ MT mice in advance of the initiation of dead cell-induced inflammation. Neutrophilic response to acetaminophen in liver tissue was also reduced in  $\mu$ MT mice and it was substantially restored by reconstitution of natural antibodies by serum transfer. [Conclusion] Natural antibodies participate in acute cell death-induced inflammation.

### ICW-B6-2

#### The relevance of serum 14-3-3 $\eta$ levels to clinical and radiographic outcomes in patients with rheumatoid arthritis

Shintaro Hirata<sup>1</sup>, Kentaro Hanami<sup>1</sup>, Kaoru Yamagata<sup>1</sup>, Ippei Miyagawa<sup>1</sup>, Satoshi Kubo<sup>1</sup>, Shunsuke Fukuyo<sup>1</sup>, Norifumi Sawamukai<sup>1</sup>, Kazuhisa Nakano<sup>1</sup>, Shingo Nakayamada<sup>1</sup>, Kazuyoshi Saito<sup>1</sup>, Anthony Marrotta<sup>2</sup>, Yoshiya Tanaka<sup>1</sup>

<sup>1</sup>The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, <sup>2</sup>Augurex Life Sciences Corp., North Vancouver, Canada

Conflict of interest: None

[Objectives] Novel biomarker is essential for better understanding of pathophysiology in rheumatoid arthritis (RA). 14-3-3 $\eta$  is an intracellular chaperone presenting in synovial fluid at high concentration in RA. Also, serum 14-3-3 $\eta$  is detectable at higher level in patients with RA than healthy individuals. However, detailed information in serum 14-3-3 $\eta$  concentration with regards to clinical disease activity, therapeutic effect, or radiographic outcome, has not been fully investigated. The objective of this study is to assess time-course of serum levels of 14-3-3 $\eta$  and their association with clinical or radiographic outcomes in RA. [Methods] Serum 14-3-3 $\eta$  (cut-off 0.19 ng/ml) was measured with custom ELISA at baseline (BL) and 1-year of treatment in 149 RA patients (ADA 49, MTX23, TCZ 50 and tofacitinib 27). Association with DAS28-ESR, CDAI, SDAI or Sharp-van der Heijde score (SHS) was assessed. [Results] BL demographics (median): age 60.0 years, disease duration 51 months, DAS28-ESR 5.35, SHS 26.5. At BL, median 14-3-3 $\eta$  was 0.70 ng/ml, positive in 110 patients (74%) with higher DAS28 [5.6 vs. 4.8,  $p=0.01$ ], CDAI [24.7 vs. 16.0,  $p=0.02$ ], or SDAI [26.8 vs. 18.8,  $p=0.02$ ]. At year-1, 14-3-3 $\eta$  reduced to 0.37 ng/ml ( $p<0.0001$ ), regardless of therapeutic, and number of positive 14-3-3 $\eta$  decreased to 97 (74%). Among 110 positive cases at BL, 18 turned to negative. 14-3-3 $\eta$  negative at year-1 was associated with preferable DAS28 category distribution (chi-sq = 11.0,  $p=0.018$ ) and less radiographic progression (chi-sq = 3.7,  $p=0.05$ ). [Conclusion] Serum 14-3-3 $\eta$  was reduced by treatment, and may correspond with clinical or radiographic outcomes in RA

### ICW-B6-3

#### The feedback loop between long noncoding RNA NRON and NFAT5 regulates the inflammatory response of rheumatoid arthritis synovial fibroblasts

Kunihiko Umekita<sup>1,2</sup>, Christoph Kolling<sup>3</sup>, Beat A Michel<sup>2</sup>, Akihiko Okayama<sup>1</sup>, Renate E Gay<sup>2</sup>, Steffen Gay<sup>2</sup>, Mojca Frank Bertoncelj<sup>2</sup>

<sup>1</sup>Division of Rheumatology, Infectious Diseases and Laboratory Medicine, Internal Medicine, University of Miyazaki, Miyazaki, Japan, <sup>2</sup>Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, <sup>3</sup>Schulthess Clinic, Zurich, Switzerland

Conflict of interest: None

[Objectives] Long noncoding RNA (lncRNA) are novel RNA transcripts, emerging as master regulators of gene expression. The lncRNA NRON, noncoding repressor of nuclear factor of activated T cells (NFAT) can repress the function of NFAT transcriptional factors. Our objective was to investigate the function of NRON in RA synovial fibroblasts (RASf) and to explore the role of NRON in the protein turnover of NFAT5. [Methods] The expression of NFAT5 protein in RA and osteoarthritis (OA) SF was analyzed by Western blotting. RASf were transfected with NRON plasmid or with small interfering RNA (siRNA) targeting NRON or NFAT5. Gene expression in RASf was measured by real-time quantitative PCR. The secretion of IL-6 was analyzed by ELISA. Immunofluorescence microscopy and Western blot of cytoplasmic and nuclear fractions were used to investigate the cytoplasmic nuclear trafficking of NFAT5 in RASf after transfection and/or TNF $\alpha$  (10ng/ml) stimulation. [Results] The levels of NFAT5 protein, NFAT5 mRNA and NRON were significantly up regulated in RASf compared to OASF. Silencing of NFAT5 in RASf led to down regulation of NRON, indicating that NFAT5 regulates the expression of NRON in RASf. Additionally, TNF $\alpha$  (2h) significantly decreased the expression of NRON in RASf; SB20912, the inhibitor of p38MAPK, however, prevented TNF $\alpha$  induced down regulation of NRON in RASf. Down regulation of NRON in RASf after silencing or TNF $\alpha$  stimulation was accompanied by the translocation of NFAT5 from the cytoplasm to the nucleus. The levels of the NFAT5 target genes, including IL6 ( $p=0.03$ ), MMP13 ( $p=0.03$ ) and JMJD3 ( $p=0.003$ ) mRNAs and IL-6 protein ( $p=0.007$ ) were significantly up regulated in RASf after silencing of NRON. Furthermore, overexpressing the lncRNA NRON in RASf significantly suppressed the TNF $\alpha$  induced expression of MMP13 ( $p=0.02$ ) and JMJD3 ( $p=0.02$ ) mRNAs. [Conclusion] The feedback loop between the lncRNA NRON and NFAT5 exists in RASf, contributing to their pathogenic characteristics in RA.

## ICW-B6-4

### Type II collagen peptide activates Akt leading to NF- $\kappa$ B up-regulation in rheumatoid arthritic chondrocytes

Tadashi Yasuda

Kobe City Medical Center General Hospital, Kobe, Japan

Conflict of interest: None

**Objectives:** In addition to cytokines, degradation products of cartilage matrix contribute to joint destruction in rheumatoid arthritis (RA). Excessive degradation of cartilage matrix in RA involves enhanced cleavage of type II collagen by collagenases, leading to an increase in proteolytic products of this collagen. A synthetic peptide derived from type II collagen (CB12-II) can induce matrix metalloproteinase (MMP)-13 with nuclear factor (NF)- $\kappa$ B activation. However, intracellular upstream events that cause NF- $\kappa$ B up-regulation in response to CB12-II remain unclear. Because Akt could stimulate signaling pathways that up-regulate the activity of NF- $\kappa$ B, this study was aimed to elucidate the involvement of Akt pathway in NF- $\kappa$ B activation by CB12-II in RA chondrocytes. **Methods:** RA cartilage specimens were obtained from the distal femur at total knee replacement surgery. Chondrocytes isolated from the cartilage were cultured in monolayer with CB12-II. Secreted levels of MMP-13 in conditioned media were determined with enzyme-linked immunosorbent assay (ELISA). The cell lysates were used to detect endogenous levels of phosphorylated Akt and phosphorylated p65 NF- $\kappa$ B by ELISA. **Results:** CB12-II stimulated MMP-13 production with up-regulation of NF- $\kappa$ B and Akt. Inhibition studies using BAY11-7085 confirmed that MMP-13 production by CB12-II was dependent on NF- $\kappa$ B pathway. Similarly, inhibition studies using LY294002 revealed that MMP-13 production by CB12-II was dependent on Akt pathway. When RA chondrocytes were preincubated with LY294002, CB12-II-induced levels of phosphorylated NF- $\kappa$ B were significantly decreased. Thus, NF- $\kappa$ B activation leading to MMP-13 production requires Akt pathway in CB12-II-stimulated chondrocytes. **Conclusion:** CB12-II activates Akt pathway leading to up-regulation of NF- $\kappa$ B in RA chondrocytes. Elucidation of intracellular pathways activated by type II collagen fragments may be helpful to understand the pathological process in RA cartilage destruction.

## ICW-B6-5

### Opposing roles of Smad2 and Smad3 as transcription cofactors of STAT3 in Th17 differentiation

Mizuko Mamura<sup>1,2</sup>, Jeong-Hwan Yoon<sup>1,2,3</sup>, Ji Hyeon Ju<sup>4</sup>, Isao Matsumoto<sup>5</sup>, Takayuki Sumida<sup>5</sup>

<sup>1</sup>Department of Molecular Pathology, Tokyo Medical University, Tokyo, Japan, <sup>2</sup>Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu, South Korea, <sup>3</sup>Department of Experimental Pathology, Graduate School of Comprehensive Human Science, University of Tsukuba, Ibaraki, Japan, <sup>4</sup>Department of Rheumatology, Catholic University of Korea, Seoul, Korea, <sup>5</sup>Division of Clinical Immunology, Major of Advanced Biomedical Applications, Graduate School of Comprehensive Human Science, University of Tsukuba, Ibaraki, Japan

Conflict of interest: None

Transforming growth factor- $\beta$  (TGF- $\beta$ ) and interleukin-6 (IL-6) are the pivotal cytokines to induce IL-17-producing CD4<sup>+</sup> T helper cells (Th17), yet their signaling network for Th17 differentiation remains largely unknown. Here we show that the highly homologous TGF- $\beta$  receptor-regulated SMADs (R-SMADs): SMAD2 and SMAD3 oppositely regulate STAT3-induced transcription of IL-17A and the retinoic acid receptor-related orphan nuclear receptor, ROR $\gamma$ t encoded by the *Rorc* gene, by acting as a transcription coactivator and corepressor of STAT3 respectively. SMAD2 phosphorylated at the serine residue 255 in its linker region interacted with STAT3 and p300 to transactivate, whereas C-terminally unphosphorylated SMAD3 interacted with STAT3 and protein inhibitor of activated STAT3 (PIAS3) to repress the *Rorc* and *Il17a* genes. Extracellular signal-regulated kinase (ERK) activated via TGF- $\beta$ , IL-6, and T cell receptor induced linker phosphorylation of SMAD2. By contrast, SMAD3 remained unphosphorylated to interact with STAT3 and PIAS3. These findings show that the novel signaling networks of STAT3 and R-SMADs regulate Th17 differentiation independently of the canonical C-terminal phosphorylation of SMAD2 and SMAD3 in distinct man-

ners.

## ICW-B6-6

### Human mesenchymal stem cells control the development of functional regulatory T cell via the IGF signaling

Ippei Miyagawa<sup>1</sup>, Shingo Nakayamada<sup>1</sup>, Kazuhisa Nakano<sup>1</sup>, Kaoru Yamagata<sup>1</sup>, Kei Sakata<sup>1</sup>, Kunihiro Yamaoka<sup>2</sup>, Koshiro Sonomoto<sup>1</sup>, Xiangmei Zhang<sup>1</sup>, Yoshiya Tanaka<sup>1</sup>

<sup>1</sup>The First Department of Internal Medicine, School of Medicine, University of Occupational & Environmental Health, Japan, Kitakyushu, Japan,

<sup>2</sup>Division of Rheumatology Department of Internal Medicine, Keio University School of Medicine, Japan

Conflict of interest: None

**[Objectives]** Human MSCs (hMSCs) possess the multipotency and immunomodulatory function. Although hMSCs induce Treg cells through production of IDO and TGF- $\beta$ , the regulatory mechanisms of functional Treg differentiation by hMSCs is unclear. **[Methods]** Human naive CD4<sup>+</sup> T cells was stimulated with anti CD3/28 antibody and cultured with or without culture supernatant of hMSCs. After 4 days, proliferation, cytokine production, expression of transcription factor and surface molecules were assessed. **[Results]** The hMSC supernatant suppressed proliferation and IFN- $\gamma$  production of CD4<sup>+</sup> T cells and induced CD4<sup>+</sup> FoxP3<sup>+</sup> Treg cells which express PD-1/PD-L1 and IGF2R. The hMSC supernatant contained a large amount of IGFBP-4 which inhibits IGF signaling, whereas the levels of TGF- $\beta$  and IGF were comparable to culture medium. IGF2 enhanced Treg function through IGF2R and neutralizing IGFBP-4 in hMSC supernatant by IGFBP-4 antibody caused induction of CD4<sup>+</sup> FoxP3<sup>high</sup> PD-L1<sup>high</sup> functional Tregs. **[Conclusion]** The hMSC inhibits the T cell proliferation and cytokine production via induction of CD4<sup>+</sup> IGF2R<sup>+</sup> Foxp3<sup>+</sup> Tregs. Further, hMSC simultaneously produces IGFBP-4 and suppress FoxP3 and PD-L1 expression on Tregs, indicating that hMSC may have passive regulatory mechanism of functional Treg cells.

## ICW-B7-1

### FPR2 is specifically expressed on Th1 cells in GPI-induced arthritis and highly expressed in patients of rheumatoid arthritis

Yuki Tanaka, Isao Matsumoto, Asuka Inoue, Naoto Umeda, Chinatsu Takai, Yuko Kurashima, Hoshimi Kawaguchi, Hiroshi Ebe, Takayuki Sumida

Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

Conflict of interest: None

**[Objectives]** CD4<sup>+</sup>T cell are critical to the pathogenesis of rheumatoid arthritis (RA). In glucose-6-phosphate isomerase (GPI) induced-arthritis (GIA), Th1 and Th17 cells are indispensable for both the induction and the effector phase. We recently identified the highly expression of formyl-peptide receptor 2 (FPR2) in splenic CD4<sup>+</sup>T cells from GIA mice by DNA microarray. To clarify the function of FPR2 in CD4<sup>+</sup> T cells in the generation of arthritis, we investigated the expression of FPR2 in GIA and FPRL-1 (human counterpart) in patients with RA. **[Methods]** (1) To determine the Th subsets expressing FPR2, we sorted FPR2<sup>+</sup> or FPR2<sup>-</sup> CD4<sup>+</sup>T cells from lymph nodes of GIA, and the mRNA expression of various markers on CD4<sup>+</sup>T cell subsets (Th1, 2, 17, Tfh and Treg) was examined. (2) We analyzed the expression of FPR2 on Th1, Th17 or Treg cells in the polarized condition in vitro. (3) To examine the production of IFN $\gamma$  from antigen-specific FPR2<sup>+</sup>CD4<sup>+</sup>T cells, recall stimulation of GPI was performed with lymph nodes from peptide-GIA. (4) In human, we analyzed the expression of FPRL-1 mRNA on PBMC and CD4<sup>+</sup> T cells from patients with RA, Sjögren's syndrome (SS) and healthy subjects (HS). **[Results]** (1) The T-bet and IFN $\gamma$  were highly expressed on FPR2<sup>+</sup>CD4<sup>+</sup>T cells than those on FPR2<sup>-</sup>CD4<sup>+</sup>T cells, whereas their marker for Th2, Th17, Tfh and Treg cells were not expressed. (2) The expression of FPR2 was frequently detected on Th1 polarized cells, but not on Th17 and Treg polarized cells. (3) The IFN $\gamma$  was produced in 25% of the GPI-specific CD4<sup>+</sup>FPR2<sup>+</sup>T cells. (4) The expression of FPRL-1 on PBMC and CD4<sup>+</sup> cells was significantly higher in patients with RA compared with HS or SS patients. **[Conclusion]** We identified that FPR2<sup>+</sup>T

cells showed Th1 phenotype in mice and FPRL-1 was highly detected on CD4<sup>+</sup>T cells in patients with RA. The FPR2<sup>+</sup>Th1 and FPRL-1<sup>+</sup>T cells might play a crucial role in the pathogenesis of GIA and RA, respectively.

### ICW-B7-2

#### **Foxp3<sup>+</sup> regulatory T cells in peripheral blood and synovial fluid of patients with rheumatoid arthritis: A comparative phenotypic and functional analysis**

Jun Saegusa<sup>1</sup>, Keisuke Nishimura<sup>1</sup>, Miwa Nishida<sup>1</sup>, Yasushi Miura<sup>2</sup>, Seiji Kawano<sup>1</sup>, Akio Morinobu<sup>1</sup>

<sup>1</sup>Department of Rheumatology and Clinical Immunology, Kobe University Hospital, Kobe, Japan, <sup>2</sup>Department of Orthopedic Surgery, Kobe University Hospital, Kobe, Japan

Conflict of interest: None

[Objectives] In contrast to the various conclusions regarding the frequency of regulatory T (Treg) cells in peripheral blood from RA patients (RAPB), there is a general agreement that the frequency of Treg cells is higher in the synovial fluid from RA patients (RASF) than that in controls. In addition, Treg cells in RASF are known to have impaired suppressive function compared to those in RAPB. A recent study has demonstrated that human Treg cells can be classified into three functionally unique subpopulations: CD45RA<sup>+</sup>Foxp3<sup>low</sup> naïve Treg cells, CD45RA<sup>+</sup>Foxp3<sup>high</sup> effector Treg cells, both of which have suppressive functions, and non-suppressive CD45RA<sup>+</sup>Foxp3<sup>low</sup>non-Treg cells. The objective of this study is to determine the characteristics of Foxp3<sup>+</sup> Treg cells in RAPB and RASF. [Methods] CD4<sup>+</sup> T cells from RAPB and RASF were classified into different subsets based on the expression of CD45RA, CCR7, CD27, and CD28 by flow cytometry. Foxp3<sup>+</sup> Treg cells were further classified into three functionally distinct subsets based on the expression of CD45RA and Foxp3. [Results] The frequency of effector Treg cells was significantly decreased in RAPB, compared to those from healthy controls. As a result of the decrease of effector Treg cells, more than half of the Foxp3<sup>+</sup> Treg cells were the non-Treg cells in RAPB. In addition, the percentage of naïve Treg cells was negatively correlated with DAS28-CRP. In RASF, most of the Foxp3<sup>+</sup> cells were non-Treg cells (81.7 ± 10.4%), and the frequency of non-Treg cells in RASF was significantly increased compared to that in RAPB. Furthermore, the non-Treg cells in CD27<sup>+</sup>CD28<sup>+</sup> effector memory T cell subset was significantly increased in RASF. [Conclusion] Our results that non-Treg cells are increased in RASF shed light on the seemingly paradoxical observations that FoxP3<sup>+</sup> Treg cells are increased in RASF. The imbalance between these FoxP3<sup>+</sup> Treg cell subsets in the circulation and at the site of inflammation may reflect the immune dysregulation in RA.

### ICW-B7-3

#### **The role of Egr2 and Egr3 on T cells in regulating humoral responses**

Kaoru Morita, Tomohisa Okamura, Mariko Inoue, Yukiko Iwasaki, Shuji Sumitomo, Keishi Fujio, Kazuhiko Yamamoto

Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Japan

Conflict of interest: None

[Objectives] Early growth response gene-2 (Egr2) and Egr3 have been regarded as essential transcriptional factors in T cell anergy induction. Egr3 is thought to compensate for the function of Egr2. Earlier studies have suggested that Egr2 is a susceptibility gene in systemic lupus erythematosus (SLE), and T- and B-cells specific Egr2/3 double conditional knock-out (DKO) mice result in lethal autoimmune inflammatory diseases. These studies raise the possibility that Egr2/3 function as important brakes on developing autoimmune diseases, especially in SLE. Although previous studies about Egr2/3 DKO mice paid attentions to Egr2/3 roles in inhibiting Th1/Th17 cytokines, the precise mechanism about regulating autoantibody productions still remains unknown. [Methods] First, we generated T-cell specific Egr2 knock out (CKO) mice (*Egr2<sup>fl/fl</sup> CD4-Cre<sup>+</sup>*) and T-cell specific Egr2/3 double knock out (DKO) mice (*Egr2<sup>fl/fl</sup> Egr3<sup>fl/fl</sup> CD4-Cre<sup>+</sup>*). Then we conducted their phenotypic and pathological analyses, and examined the changes of T-cell subsets by flow cytometry. Next, we assessed the gene or cytokine expression profiles in T-cells from Egr2/3 DKO mice and evaluated the roles of Egr2/3 in the regulation of

autoimmunity. [Results] Egr2/3 DKO mice developed early onset lupus-like syndromes manifested by glomerulonephritis and high titers of anti-dsDNA antibodies compared to Egr2 CKO mice. We detected excess accumulation of T follicular helper cells (Tfh) and germinal center B cells in Egr2/3 DKO mice. We also found dysregulated function of CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup> regulatory T cells (LAG3<sup>+</sup> Tregs) which highly express Egr2, and transferring LAG3<sup>+</sup> Tregs from wild-type mice into Egr2/3 DKO mice could partially rectify the excess Tfh accumulation. [Conclusion] Our results reveal that Egr2/3 have important roles in regulating Tfh differentiation and LAG3<sup>+</sup> Treg function. The unique attributes of Egr2/3 in T cells may provide a useful pathway for manipulating the treatment of autoimmune disorders.

### ICW-B7-4

#### **The regulatory function of the CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup> T cells in vitro and the characteristics in patients with rheumatoid arthritis in the presence of Abatacept**

Shinichiro Nakachi, Shuji Sumitomo, Yumi Tsuchida, Rika Kato, Keiichi Sakurai, Norio Hanata, Haruka Tsuchiya, Yasuo Nagafuchi, Hirofumi Shoda, Kazuyoshi Ishigaki, Kensuke Yamaguchi, Tomohisa Okamura, Keishi Fujio, Kazuhiko Yamamoto

Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Japan

Conflict of interest: Yes

[BACKGROUND and OBJECTIVES] We previously confirmed that CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup> T cells (CD25<sup>+</sup>LAG3<sup>+</sup> T cells) produce IL-10 and suppressed B cell antibody production. The characteristics and the function of CD25<sup>+</sup>LAG3<sup>+</sup> T cells have not been clarified in human. We set the purpose onto elucidating the regulatory function of CD25<sup>+</sup>LAG3<sup>+</sup> T cells in vitro and clarifying the proportion of the subset in peripheral blood mononuclear cells (PBMCs) taken from healthy donors and patients with rheumatoid arthritis (RA), in particular, focusing on Abatacept (ABT) treatment. [METHODS] PBMCs were taken from 86 patients with RA from the University of Tokyo Hospital and 94 healthy donors, and regulatory T cell subsets were analyzed by FACS. In addition, 15 patients were evaluated before and after ABT treatment. Moreover, we concurrently performed functional analysis of CD25<sup>+</sup>LAG3<sup>+</sup> T cells and observed the effect on cultured CD25<sup>+</sup>LAG3<sup>+</sup> T cells in the presence of ABT. [RESULTS] The frequency of CD25<sup>+</sup>LAG3<sup>+</sup> T cells was lower in RA patients with severe disease activity than compare with RA patients with mild disease activity (P value = 0.02 Mann-Whitney test). Surprisingly, the frequency of CD25<sup>+</sup>LAG3<sup>+</sup> T cells significantly increased and that of CD25<sup>+</sup> Tregs significantly decreased after six months treatment with ABT (P value = 0.00256 and 0.0215, respectively, Wilcoxon signed-rank test). In in vitro experiments, CD25<sup>+</sup>LAG3<sup>+</sup> T cells from healthy donors produced extremely high IL-10 protein and suppressed antibody production by B cells. Intriguingly, addition of ABT significantly preserved the expression of LAG3 protein on in vitro stimulated CD25<sup>+</sup>LAG3<sup>+</sup> T cells compared with control. [CONCLUSION] Similar to murine CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup> T cells, human CD25<sup>+</sup>LAG3<sup>+</sup> T cells produce large amount of IL-10 protein and suppress B cell antibody production. There is a possibility that ABT augments the expression of LAG3 on CD4<sup>+</sup> T cells to induce CD25<sup>+</sup>LAG3<sup>+</sup> T cells and disease amelioration.

### ICW-B7-5

#### **Monocarboxylate transporter 4, associated with the acidification of synovial fluid, is a novel therapeutic target of inflammatory arthritis**

Wataru Fujii<sup>1</sup>, Hidetake Nagahara<sup>1</sup>, Yuji Kukida<sup>1</sup>, Kazuki Fujioka<sup>1</sup>, Takahiro Seno<sup>1,2</sup>, Aihiro Yamamoto<sup>1</sup>, Masataka Kohno<sup>1</sup>, Ryo Oda<sup>1</sup>, Daisaku Tokunaga<sup>3</sup>, Toshikazu Kubo<sup>2,3</sup>, Yutaka Kawahito<sup>1</sup>

<sup>1</sup>Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>2</sup>Department of Rheumatic Diseases and Joint Function, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>3</sup>Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: None

[Objectives] We have previously reported that increased monocar-



boxylate transporter (MCT) 4 in rheumatoid arthritis synovial fibroblasts (RASFs) is associated with the acidification of synovial fluid pH in RA patients and the proliferation of RASFs *in vitro*. However, the function of MCT4 *in vivo* remains unknown. We investigate the function of MCT4 *in vivo* using a collagen-induced arthritis (CIA) mouse model. [Methods] We investigated the expression of MCT4 in inflamed joints of CIA mice by immunohistochemistry. Next, we performed electro-transfer of siRNAs to suppress the gene expression in the articular synovium. We confirmed the efficient transduction of siRNA using 6-carboxyfluorescein (FAM) labeled siRNA. We injected siRNAs specific for MCT4 into the knee joint and electric field was applied subsequently at the joint to suppress MCT4 expression. For histological analysis, mice were sacrificed 72 hours after the electro-transfer of MCT4 siRNA and the knee joints were collected. We estimated the severity of arthritis using H&E staining when MCT4 gene was knocked down in the articular joints of CIA mice. [Results] The protein levels of MCT4 were significantly increased in the articular synovium of CIA mice compared to those of control mice. The labeled siRNA was present at the intra-articular synovial tissues as revealed by fluorescence stereomicroscope. Histological assessment revealed that the severity of arthritis was decreased when MCT4 expression was suppressed by electro-transfer of siRNAs in the articular joints. [Conclusion] The protein levels of MCT4 are increased in the inflamed joints of CIA mice as well as those in RA synovium. Silencing of MCT4 decreases the severity of arthritis in CIA mice, suggesting that MCT4 is a potential therapeutic target of inflammatory arthritis.

### ICW-B7-6

#### **Nrf2 is highly expressed in synovial tissue of patients with rheumatoid arthritis and reflects their anti-oxidant potential**

Naoki Kondo<sup>1</sup>, Takahiro Netsu<sup>1</sup>, Junichi Fujisawa<sup>1</sup>, Katsumitsu Arai<sup>2</sup>, Naoto Endo<sup>1</sup>

<sup>1</sup>Division of Orthopaedic Surgery, Department of Regenerative and Transplant Medicine, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, <sup>2</sup>Division of Orthopaedic Surgery, Niigata Prefectural Chuo Hospital, Joetsu, Japan

Conflict of interest: None

[Objective] NF-E2-related factor 2 (Nrf2) is main transcription factor for anti-oxidative stress response. The defect of Nrf2 induces more severe arthritis (Wruck CJ, Ann Rheum Dis 70; 844-50, 2011). The aim of this study was to evaluate the expression level of mRNA and protein of Nrf2 and their association with CRP, ESR, and BAP (biological anti-oxidant potential) in RA cases. [Methods] Synovia were isolated from 45 cases of RA on surgery such as synovectomy and arthroplasties. Of these, biologics were treated in 10 (etanercept in 6, tocilizumab in 2, and infliximab in 1, and adalimumab in 1). Four OA patients were prepared as the control group, and their synovia were isolated on total knee arthroplasty. RNA was purified and Nrf2 mRNA expression level in synovium was semi quantified using real-time PCR. In addition, immunohistochemical staining of Nrf2 protein was performed and the percentage of Nrf2-positive cells was evaluated depending on the method as previously reported (Xu Y, Oncol Rep 25;599-607,2011). In RA cases, each sample of serum is subjected to BAP test to evaluate antioxidant capacity using Free radical elective evaluator (Diacron, Italy). Correlation analysis was performed between Nrf2 mRNA expression level and CRP, ESR, and BAP. SPSS software (Ver.21) was used for statistical analysis. [Results] Nrf2 mRNA expression level in synovia of RA cases (2.4) were significantly higher than that in OA cases (1.5). Immunopositivity of Nrf2 protein showed that 62 % of RA cases were more than moderately positive and that no case OA cases was more than moderately positive. There was no correlation between nrf2 mRNA and CRP, and nrf2 mRNA and ESR. However, BAP value was significantly correlated with nrf2 mRNA level ( $r=0.389$ ,  $p<0.05$ ). Biologics did not influence the expression level of Nrf2. [Conclusion] Nrf2 is highly upregulated in patients with RA and it reflects their anti-oxidant potential. Biologics neither downregulated Nrf2 level nor anti-oxidant potential.

### ICW-B7-7

#### **TET3-mediated epigenetic alteration in Rheumatoid arthritis fibroblast-like synoviocytes**

Kazuhisa Nakano, Kaoru Yamagata, Shingo Nakayamada, Akio Kawabe,

Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Conflict of interest: None

[Objectives] RA FLS exhibit aggressive behavior that contributes to the cytokine milieu and joint destruction. We previously reported the unique DNA methylation pattern in RA FLS and that persistent exposure of pro-inflammatory cytokines contribute to passive DNA demethylation through decreased expression of DNMT in FLS. We here assessed the involvement of a novel DNA demethylation enzyme, Ten-eleven-translocation (TET), in cytokine-mediated activation of RA-FLS. [Methods] Gene expression was determined by qPCR and protein expression by Western blot and immunostaining. 5hmC was determined by dot blot. Secretion of cytokines and MMPs was measured by CBA and latex agglutination method. Cell migration was assessed using a scratch assay. [Results] TET3 is co-expressed with CD55 in the intimal lining layer of synovium in patients with active RA. Although unstimulated RA and OA FLS expressed similar amounts of TET3 mRNA, stimulation with TNF $\alpha$  (10 ng/ml) and IL-1 $\beta$  (1 ng/ml) for 2 hrs significantly increased TET3 mRNA expression in FLS (>3-fold and >4-fold respectively). TET3 protein expression in nucleus in RA FLS were significantly increased by stimulation with TNF $\alpha$  within 48 hrs. 5-hmC was also increased when FLS were cultured continuously for 96 hrs with TNF $\alpha$ . TET3-knockdown of FLS with siRNA not only inhibited TNF-induced expression of key migratory genes, including CCL2 and ICAM-1, but also reduced TNF-induced FLS-migration completely. [Conclusion] We demonstrated that a novel DNA methylation enzyme TET3 is characteristically induced in RA FLS through TNF/IL-1 stimulation. Taken together with our previous report, persistent exposure to pro-inflammatory cytokines in the synovium not only decreases DNMT expression but also increases TET3 expression, resulting in aggressive behavior of FLS via DNA demethylation. Our study suggests that targeting the TET3-5hmC pathway may be a therapeutic strategy for preventing FLS from TNF-mediated imprinting in RA.

### ICW-B8-1

#### **Characteristic expression of chemokine receptor on B cells and its pathological relevance in patients with SLE**

Maiko Yoshikawa, Shingo Nakayamada, Shigeru Iwata, Satoshi Kubo, Naoki Yunoue, Peggy Wang, Kazuhisa Nakano, Kazuyoshi Saito, Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Conflict of interest: None

**Objectives:** SLE is characterized by an expanded population of peripheral memory B cells. However, little is known about the qualitative abnormality of B cells associated with pathogenesis of SLE. We assessed the subset classification of B cells and its pathological relevance in SLE. **Methods:** PBMCs obtained from subjects with 56 SLE, 31 RA and 8 healthy donors (HD) were analyzed. B cells and T cells were categorized by expression of chemokine receptors such as CXCR3, CXCR5 and CCR6. The results were correlated with the clinical disease activity index and the titer of autoantibodies such as anti-dsDNA and anti-Sm antibody. **Results:** 1) The proportion of CD19<sup>+</sup>CD20<sup>+</sup>CXCR5<sup>+</sup> B cells has significantly increased in SLE compared to HD and RA. Those tendency was remarkably noted in IgD<sup>+</sup>CD27<sup>+</sup> memory B cells ( $p<0.01$ ). 2) The population was not correlated with disease activity index, whereas it was positively correlated with the proportion of activated Tfh cells ( $p<0.05$ ). 3) CXCR5<sup>+</sup>CXCR3<sup>-</sup> B cells were positively correlated with anti-Sm antibody, and CXCR5<sup>+</sup>CXCR3<sup>+</sup> memory B cells were positively correlated with the proportion of effector memory T cells ( $p<0.05$ ). 4) CXCR5<sup>+</sup> memory B cells still remained after improvement of disease activity by immunosuppressive therapy ( $p<0.05$ ). **Conclusion:** The results revealed that pathological effector B cells, which lose CXCR5 and express CXCR3, play important roles in autoantibody production through the interaction with Tfh cells in SLE patients. In addition, the results revealed that this population still remained after improvement of disease activity by immunosuppressive therapy, indicating the pathological B cell differentiation may underlie independent of disease activity in etiology of SLE and needs to be borne in mind in the design of new therapeutic strategies

for this disease.

### ICW-B8-2

#### Cell cycle related gene signature and interferon inducible gene signature in circulating CD38<sup>+</sup>CD43<sup>+</sup> B cell subset in SLE

Hiroshi Fujii, Tomoaki Machiyama, Kanae Akita, Yukiko Kamogawa, Ryu Watanabe, Yoko Fujita, Yuko Shiota, Tomonori Ishii, Hideo Harigae  
Department of Hematology and Rheumatology, Tohoku University, Sendai, Japan

Conflict of interest: Yes

[Objectives] The percentage of CD38<sup>+</sup>CD43<sup>+</sup> B cell subset is significantly increased in pre-treatment SLE than post-treatment SLE and healthy controls (HC). The majority of CD38<sup>+</sup>CD43<sup>+</sup> B cells belong to conventional plasmablast, CD19<sup>lo</sup>CD27<sup>hi</sup> B cells. To clarify the biological properties of the CD38<sup>+</sup>CD43<sup>+</sup> B cell subset in SLE, gene profiling of purified CD38<sup>+</sup>CD43<sup>+</sup> B cells, naïve B cells, memory B cells from SLE patients and HC were compared by microarray. [Method] Naïve B cells (CD19<sup>+</sup>CD27<sup>+</sup>CD38<sup>+</sup>CD43<sup>-</sup>), memory B cells (CD19<sup>+</sup>CD27<sup>+</sup>CD38<sup>+</sup>CD43<sup>+</sup>) and CD19<sup>+</sup>CD38<sup>+</sup>CD43<sup>+</sup> B cells were sorted with FACS Aria II from SLE and HC (n=4, respectively). Total RNA were isolated and labelled, then mRNA levels were analyzed with Agilent microarray. Gene expression data was analyzed with GeneSpring and Ingenuity Pathway Analysis software. Statistic analysis was performed in comparative analysis between SLE and HC in each B cell subset by modified t-test, and in canonical pathway analysis by Fisher's exact test. Normalized gene expression values of IFN gene signature (23 genes) and cell cycle related gene signature (253 genes) were summed to estimate the gene expression scores. [Results] Analysis of significantly increased and decreased genes in each B cell subset between SLE and HC showed that interferon signaling pathway was up-regulated among significantly changed genes in all naïve, memory, CD19<sup>+</sup> CD38<sup>+</sup> CD43<sup>+</sup> B cell subsets, in contrast, cell cycle related pathways were increased in only CD19<sup>+</sup> CD38<sup>+</sup> CD43<sup>+</sup> B cell subset. Gene expression scores of IFN inducible gene signature were significantly higher in all B cell subsets of SLE than HC, whereas gene expression scores of cell cycle related gene signature were significantly higher only in CD19<sup>+</sup> CD38<sup>+</sup> CD43<sup>+</sup> B cell subset. [Conclusion] Circulating CD38<sup>+</sup> CD43<sup>+</sup> B cells of SLE have both of more IFN inducible genes and more cell cycle related genes than that of HC. This might be a novel clue to specific plasmablast targeting therapy for SLE.

### ICW-B8-3

#### Depletion of CD4<sup>+</sup>CD25<sup>+</sup>LAG-3<sup>+</sup>Egr2<sup>+</sup> regulatory T cells using DNA vaccination results in lupus-like severe systemic autoimmunity

Shuji Sumitomo, Keishi Fujio, Tomohisa Okamura, Kazuyoshi Ishigaki, Yukiko Iwasaki, Kaoru Morita, Hirofumi Shoda, Mihoko Shibuya, Kazuhiko Yamamoto  
Department of Allergy and Rheumatology, The University of Tokyo, Graduate School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] CD4<sup>+</sup>CD25<sup>+</sup>LAG-3<sup>+</sup> T cells are newly reported regulatory T cell subset that plays a significant role in suppressing peripheral inflammation and specifically expresses the transcription factor Egr2. Although the lack of LAG-3 molecule is expected to induce autoimmunity, LAG-3-deficient mice present minimal immunopathological change. I tried to deplete CD4<sup>+</sup>CD25<sup>+</sup>LAG-3<sup>+</sup> regulatory T cells using immunological procedure in wild type mice and analyzed its sequelae *in vivo*. [Methods] In order to deplete CD4<sup>+</sup>CD25<sup>+</sup>LAG-3<sup>+</sup> T cells, I adopted DNA vaccination procedure. We generated the pCAGGS-LAG3 vector construct that contained LAG3 cDNA sequence. For DNA vaccination, we injected intravenously pCAGGS-LAG3 vector into C57B/L6 mice, and analyzed their phenotype after several months. [Results] After several months, pCAGGS-LAG3 vector injected mice developed severe dermatitis, proteinuria, and high titer of anti ds-DNA antibody, while control pCAGGS vector injected mice were normal. Pathological analysis revealed revealed glomerulonephritis with IgG/C3 deposition and dermatitis with epidermal hyperplasia, hyperkeratosis and mononuclear cell infiltration. In FACS analysis, pCAGGS-LAG-3 injected mice with severe lupus-like lesion presented the depletion of CD4<sup>+</sup>CD25<sup>+</sup>LAG-3<sup>+</sup>Egr2<sup>+</sup> T cells. More-

over, serum ELISA in these mice revealed high titer of anti-LAG-3 antibody. [Conclusion] DNA vaccination with pCAGGS-LAG-3 was considered to be the main cause of anti-LAG-3 antibody production and the depletion of CD4<sup>+</sup>CD25<sup>+</sup>LAG-3<sup>+</sup>Egr2<sup>+</sup> T cells, which is responsible for the development of lupus-like lesions. This is the first report about the procedure of efficient CD4<sup>+</sup>CD25<sup>+</sup>LAG-3<sup>+</sup>Egr2<sup>+</sup> T cells depletion.

### ICW-B8-4

#### Discovery of E3 Ubiquitin-protein Ligase TRAF 7 as a Potential Biomarker for Systemic Lupus Erythematosus

Shir-Ly Huang<sup>1</sup>, Rashmi Madda<sup>1</sup>, Shih-Chang Lin<sup>2</sup>

<sup>1</sup>National Central University, Zhongli City, Taiwan, <sup>2</sup>Cathy General Hospital, Taipei, Taiwan

Conflict of interest: None

Human rheumatic autoimmune diseases are common in the general population. The severity and the prevalence, diagnosis, mechanism, activity of the diseases and effects on the organs prediction has sometimes been very difficult to be evaluated. This is mainly due to the broad clinical manifestations in terms of subclinical symptoms which show the disease involvement to multiple organs. Specific laboratory and diagnostic tools for the treatment and diagnosis of the rheumatic diseases like systemic lupus erythematosus (SLE), rheumatoid arthritis and other autoimmune disorders are lacking. Therefore, we aimed to focus on the discovery of novel biomarkers discovered by using gel-based proteomics and the identified by mass spectrometric analysis. Samples were collected from the healthy individuals and SLE patients in Taiwan, which are also female sufferers of chronic kidney disorders. The serum proteomic expression level between the two groups were compared by gel electrophoresis and image analysis. The results demonstrated that tumor necrosis receptor associated factor (TRAF) superfamily protein, E3 ubiquitin protein ligase TRAF 7, showed a higher expression level variance in the patient samples. Latest evidences by other teams provide interesting details related to this protein about its unique structure and involvement in various critical signaling cascades and regulatory events like multimerization, ubiquitination, necrosis and apoptosis. Due to these reasons the protein may be released into the plasma and may involve in the pathogenic or disease activity of the particular illness. The expression level of TRAF 7 is 1.4 fold higher than the normal individuals and it has been further confirmed quantitatively under enzyme-linked immune sorbent assay with another set of SLE patients and controls. It is the first time we are reporting that TRAF 7 protein can be endorsed as a potential biomarker and employed as a diagnostic tool for SLE disease activity.

### ICW-B8-5

#### Immunoregulatory roles of the novel anti-inflammatory cytokine interleukin-35 in systemic lupus erythematosus mouse

Zhe Cai<sup>1</sup>, Chun Kwok Wong<sup>1</sup>, Lai Shan Tam<sup>2</sup>

<sup>1</sup>Department of Chemical Pathology, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong, <sup>2</sup>Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong

Conflict of interest: Yes

[Objectives] The immunomodulatory role of the novel anti-inflammatory cytokine IL-35 in the MRL/MpJ-Fas<sup>lpr</sup>/2J SLE mouse. [Methods] Plasma concentrations of IL-35 and its receptor, and disease associated parameters were measured using ELISA. Expression of IL-35 receptor subunits IL-12Rβ2 and gp130 on the CD4<sup>+</sup> helper (Th) cells and CD19<sup>+</sup> B cells, and the number of CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> Treg and IL-10<sup>+</sup>CD19<sup>+</sup>CD5<sup>+</sup>CD1d<sup>+</sup> Breg cells were quantitated by flow cytometry. The *ex vivo* effect of IL-35 on the lymphocytes produced cytokines were tested by luminex multiplex assay. The mRNA expression of IL-35 related molecules, mouse Th cell differentiation and JAK/STAT signaling pathway were detected by RT-qPCR and PCR array. Histopathological assessment were examined microscopically. [Results] SLE mice were observed clinical manifestations include proteinuria, lymphadenopathy, skin lesion and glomerulonephritis compared with healthy controls (HC). Consistent with the clinical parameters, the %Breg cells in thymus of SLE mice were significantly higher than HC and IL-35 treated SLE mice.

the %Breg cells in spleen of control mice with IL-35 treatment were significantly increased and higher than SLE mice. However, the %CD4<sup>+</sup>CD25<sup>+</sup>Treg were significantly decreased in spleen and thymus of SLE mice than HC. [Conclusion] Results of this *in vivo* SLE animal model may also furnish a biochemical basis for the development of potential therapeutic target of IL-35 for the treatment of autoimmune-mediated inflammation.

### ICW-B8-6

#### Circulating Tfh cells mediate CD27+IgG+B cell activation through IL-21 in patients with systemic lupus erythematosus

Zhen Chen<sup>1</sup>, Meng-Tao Li<sup>1</sup>, Dong Xu<sup>1</sup>, Jiu-Liang Zhao<sup>1</sup>, Ting Wang<sup>1</sup>, Heng-Hui Zhang<sup>2</sup>, Xiao-Feng Zeng<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China, <sup>2</sup>Peking University People's Hospital, Peking University Hepatology Institute, Beijing Key Laboratory of Hepatitis C and Immunotherapy for Liver Diseases, Beijing, China

Conflict of interest: None

[Objective] Systemic lupus erythematosus (SLE) is associated with B cell subsets skewing and activation. The activation and differentiation of B cells are regulated by CD4<sup>+</sup>T cells, especially by follicular helper T (Tfh) cell, a T cell subset associated with interleukin (IL)-21 secretion. However, whether Tfh cells are associated with IgG+B cells in patients with SLE remains largely unknown. [Methods] A total of 37 newly-diagnosed SLE patients and 21 age and gender matched healthy controls (HC) were enrolled for this study. The frequency of IgG+B cells including CD27+IgG+B cells, the expression of activation makers including CXCR3, CD86 and CD95 on IgG+B cells, and the percentage of circulating Tfh subsets cells were analyzed by flow cytometry. The role of Tfh cells on the activation of IgG+B cells was investigated in a co-culture system. [Results] The frequency of CD27+IgG+B cells reduced in SLE patients in comparison with HC, while the activation of CD27+IgG+B cells increased with elevated expression of CD95, CD86 and CXCR3. The percentage of CD27+IgG+B cells was positively correlated with the level of anti-dsDNA autoantibodies. Meanwhile, circulating Tfh cells (CD4<sup>+</sup>CXCR5<sup>+</sup>PD-1<sup>+</sup>), Tfh2 cells (IL-4<sup>+</sup>CXCR5<sup>+</sup>) and Tfh17 cells (IL-17<sup>+</sup>CXCR5<sup>+</sup>) as well as Tfh21 cells (IL-21<sup>+</sup>CXCR5<sup>+</sup>) were significantly expanded in SLE patients. Circulating Tfh cells from SLE patients were better able to promote the expressions of CD86 and CD95 on CD27+IgG+B cells compared with those in HC in co-culture system. Blocking with IL-21 with IL-21R FC Chimera, the expression of CD86 and CD95 on CD27+IgG+B cells induced by Tfh cells decreased in SLE patients. [Conclusion] The IgG+B cell abnormalities induced by SLE were associated with decreased frequency and increased activation of CD27+IgG+B cells in SLE patients. The frequencies of circulating Tfh cells and different Tfh subsets increased in SLE patients. Tfh cells mediated the activation of IgG+CD27+ B cells through IL-21 in SLE patients.

### ICW-B9-1

#### The diversity of lymphocyte subsets and pathogenesis in systemic lupus erythematosus (SLE)

Satoshi Kubo<sup>1</sup>, Shingo Nakayama<sup>1</sup>, Naoki Yunoue<sup>1</sup>, Maiko Yoshikawa<sup>1</sup>, Yusuke Miyazaki<sup>1</sup>, Kei Sakata<sup>2</sup>, Kazuhisa Nakano<sup>1</sup>, Kazuyoshi Saito<sup>1</sup>, Yoshiya Tanaka<sup>1</sup>

<sup>1</sup>The 1st Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, <sup>2</sup>Mitsubishi Tanabe Pharma Corporation

Conflict of interest: None

[Objectives] SLE is an autoimmune disease characterized by overproduction of autoantibodies by B cells and breaking self-tolerance of T cells. However, little is known about the relationship between these immune cells in the etiology of SLE. Here, we investigate the interactive activation between B cells and helper T cells in the pathogenesis of SLE. [Method] 39 SLE patients and 26 healthy donors (HD) were enrolled in this study. Circulating lymphocyte subsets were defined based on comprehensive flow cytometric analysis for human immune system termed 'the Human Immunology Project' established by NIH/NIAID. [Results]

The proportions of central memory B cell (15% vs 26%), effector B cell (5% vs 11%), and plasmablasts (4% vs 16%) were higher, whereas the proportion of IgM memory B cell (25% vs 12%) was lower in SLE compared with HD. For T cell subsets, the proportion of Tfh (0.8% vs 1.5%) and Treg (5% vs 7%) was higher in SLE, whereas the proportion of Th1 (18% vs 19%) and Th17 (11% vs 13%) was not different. To assess whether these subset shaped the immunological features of SLE, we calculated the Pearson product-moment correlation coefficient among these subsets and also conducted correlation clustering analysis. Tfh correlated with Th1 and plasmablast while activated Treg correlated with activated Th17 and IgM memory B cells. We also investigated the correlation between these cells and clinical findings. Although T cell subset did not correlate with clinical findings, IgM memory B cells negatively correlated with BILAG index. However, in patients with high proportion of Tfh, Tfh correlated positively with BILAG index. Likewise, activated Treg correlated negatively with SLEDAI in patients with low proportion of Tfh. [Conclusion] The impaired balance of Tfh-Th1-plasmablast axis and Treg-Th17-IgM memory B cell axis contribute to pathogenesis of SLE. Comprehensive analysis of lymphocyte subset revealed the heterogeneity of SLE and may provide a personalized medicine.

### ICW-B9-2

#### Experimentation about subsets of peripheral blood mononuclear cells in active systemic lupus erythematosus

Jun Kikuchi<sup>1</sup>, Masaru Takeshita<sup>1</sup>, Katsuya Suzuki<sup>1</sup>, Yoshiaki Kassai<sup>2</sup>, Takahiro Miyazaki<sup>2</sup>, Tsutomu Takeuchi<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan, <sup>2</sup>Inflammation Drug Discovery Unit, Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited, Kanagawa, Japan

Conflict of interest: Yes

**OBJECTIVE:** To examine the abnormality of cell-surface expressions in peripheral blood mononuclear cells (PBMC) in active systemic lupus erythematosus (SLE) patients. **METHODS:** PBMC subsets and activation markers were quantified using a whole blood flowcytometry in 10 SLE patients who gave informed consent for this study and 38 normal healthy controls (NHC). We compared the proportions of PBMC subsets in SLE patients with those in NHCs and analyzed relations with clinical characteristics in SLE patients. **RESULTS:** Mean age was 44.9 and 39.8 years old in SLE patients and NHCs, respectively. All candidates were female. Mean SLE Disease Activity Index was 13. The blood samples of all 10 SLE patients were collected before they received induction therapies. 7 patients were treatment-naïve, and the other 3 patients were treated with mean 5 mg/day of oral prednisolone and 2 patients of the 3 patients were treated with concomitant immunosuppressant. The proportion of effector memory T cells in CD4<sup>+</sup> T cells and HLA-DR expression on CD4<sup>+</sup> T cells were higher in SLE patients than in NHCs (p=0.002 and p=0.007). The proportions of IgD+CD27+ memory B cells, IgD+CD38+ B cells and IgD+CD38- B cells in all B cells were lower in SLE patients (p<0.001, p=0.016 and p=0.019, respectively). The proportion of CD38++IgD- germinal center B cells in B cells was higher in SLE patients (p<0.001), and especially the proportion was higher in patients with skin lesions among SLE patients (p=0.025). The proportion of plasmablast was higher (p<0.001), and the number inversely correlated with the titer of serum CH50 (p=0.044, ρ=-0.77). **CONCLUSIONS:** The proportions of peripheral differentiated B cell subsets were higher in active SLE patients and a part of them correlated with skin lesions of SLE

### ICW-B9-3

#### Analysis of CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup>T cells in lupus patients

Rika Kato, Shuji Sumitomo, Shinichiro Nakachi, Yumi Tsuchida, Keiichi Sakurai, Norio Hanata, Haruka Tsuchiya, Yasuo Nagafuchi, Hirofumi Shoda, Hiroko Kanda, Shoko Tateishi, Tomohisa Okamura, Keishi Fujio, Kazuhiko Yamamoto

The University of Tokyo Hospital, Tokyo, Japan

Conflict of interest: Yes

[Objectives] We previously identified IL-10-producing CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup>Treg (LAG3<sup>+</sup>Treg) that play an important role in the control of

lupus model mouse. In addition, human LAG3<sup>+</sup> Treg shared suppressive activity with murine LAG3<sup>+</sup> Treg. Based on these findings, we here examined the character of CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup> T cells. **[Methods]** We collected peripheral blood mononuclear cells (PBMCs) from 24 SLE patients, 24 RA patients and 24 healthy donors and quantitated the frequency of naïve T cells, CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup> T cells, CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup> T cells, CD4<sup>+</sup>CD25<sup>+</sup>CD127<sup>low</sup>Treg and Memory T cells in CD4<sup>+</sup> T cells by FACS. The correlations between these subsets and SLEDAI, complement and anti-ds-DNA antibody titers were examined. Also we analyzed the alterations in these subsets after the treatment in SLE patients. Moreover, we examined mRNA expressions and cytokine secretions of these subsets. **[Results]** CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup> T cells exhibited a significant increase in SLE patients compared to RA patients and healthy controls. The expression of IL-10 was significantly higher than that of CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup> T cells. The frequency of CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup> T cells in SLE patients showed a reduction after treatment and an increase upon relapse. The percentages of each subset in CD4<sup>+</sup> T cells had no relationship with clinical index. CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup> T cells from healthy donor expressed high-levels of IL-10 in vitro. On the other hand, this subset also expressed genes associated with Th17 and Th1 cells. **[Conclusion]** CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup> T cells, which are frequently detected in SLE patients, not only expressed IL-10 but also have some features of Th1/Th17 cells, suggesting the association between effector T cells and CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup> T cells. Further examination is required to find out the function of this subset in SLE patients.

### ICW-B9-4

#### Immunopathological roles of the novel inflammatory cytokine interleukin-36 in patients with systemic lupus erythematosus

Man Chu<sup>1</sup>, Chun Kwok Wong<sup>1</sup>, Wai Kai Lam<sup>1,2</sup>, Lai Shan Tam<sup>3</sup>

<sup>1</sup>Department of Chemical Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China, <sup>2</sup>State Key Laboratory of Quality Research in Chinese Medicine, Macau Institute for Applied Research in Medicine and Health, Macau University of Science and Technology, Taipa, Macau, <sup>3</sup>Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong

Conflict of interest: None

**[Objectives]** To investigate immunopathological roles of novel inflammatory cytokine IL-36 in patients with systemic lupus erythematosus (SLE). **[Methods]** Forty-five Chinese SLE patients and fifteen age- and sex- matched control subjects were recruited in rheumatology clinic, Prince of Wales Hospital, Hong Kong. The expression of these cytokines and their putative receptors of peripheral blood mononuclear cells (PBMC) were determined by flow cytometry and quantitative RT-PCR in SLE patients and control subjects. *Ex vivo* production of cytokines and chemokines stimulated by IL-36 cytokines were determined by Multiplex assay reagent. **[Results]** The expression of IL-36R was significantly up-regulated on the cell surface of B cells in severe and moderate SLE patients compared with normal controls (NCs) (both  $p < 0.05$ ). The frequency of CD3<sup>+</sup>IL-22<sup>+</sup>IL-17<sup>+</sup> T helper 17 (Th17) cells was significantly higher in moderate and severe SLE patients compared with NCs (both  $p < 0.001$ ). The frequency of regulatory B (Breg) cells was significantly decreased in mild ( $p < 0.01$ ), moderate ( $p < 0.001$ ) and severe ( $p < 0.001$ ) SLE patients compared with NCs. IL-36 $\alpha$  mRNA expression of PBMC were significantly lower in SLE patients including mild, moderate and severe SLE groups than that in NCs (all  $p < 0.01$ ). The mRNA expression of IL-36 $\alpha$ , IL-36 $\gamma$  and novel related IL-1 family inflammatory IL-38 of PBMC were positively correlated with IL-36R (all  $p < 0.0001$ ), and mRNA expression of IL-36 $\alpha$  and IL-36 $\gamma$  positively correlated with IL-38 in SLE patients (all  $p < 0.0001$ ). With the stimulation of IL-36 $\alpha$ , IL-36 $\beta$  and IL-36 $\gamma$ , *ex vivo* production of IL-10, IL-6, CCL-2, CXCL-8, IL-1 $\beta$ , but not Th1 cytokine interferon- $\gamma$ , significantly increased in SLE patients comparing with NCs (all  $p < 0.05$ ). **[Conclusion]** Results of this cross-sectional clinical study may imply the potential immunoregulatory roles of IL-36 in SLE and shed light on a potential therapeutic modality of SLE.

### ICW-B9-5

#### Soluble CD146 in cerebrospinal fluid of patients with neuropsychiatric systemic lupus erythematosus

Lingling Zhang<sup>1</sup>, Li Zhang<sup>1</sup>, Mengtao Li<sup>1</sup>, Hongxia Duan<sup>2</sup>, Xiyun Yan<sup>2</sup>, Xiaofeng Zeng<sup>1</sup>

<sup>1</sup>Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China, <sup>2</sup>Key Laboratory of Protein and Peptide Pharmaceutical, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China

Conflict of interest: None

**[Objectives]** The aim of this study was to investigate the possible link between soluble CD146 (sCD146) and disease activity of NPSLE. **[Methods]** All patients from the Peking Union Medical College Hospital, a total of 70 patients fulfilling the criteria of the ACR for SLE classification were selected. NPSLE was diagnosed under the ACR criteria for neuropsychiatric lupus syndromes. In all, 61 patients were diagnosed with NPSLE and 9 patients did not fulfill our criteria for NPSLE. Of the 61 patients with NPSLE, samples were collected from 10 patients before NPSLE treatment, whereas samples from the remaining 51 patients were collected during or after glucocorticoid treatment specifically for neuropsychiatric symptoms. Moreover, 34 patients without any CNS in their MRI or CNS viral infection or with brain cancer metastases were used as controls. Levels of sCD146 in the cerebrospinal fluid (CSF) and the serum were determined using an ELISA. **[Results]** sCD146 were significantly elevated in the CSF of patients with NPSLE (25.88 $\pm$ 1.40 ng/ml) compared with that of diseases control (10.52 $\pm$ 0.71 ng/ml,  $P < 0.001$ ). However, the serum level of sCD146 in NPSLE (165.7 $\pm$ 8.69 ng/ml) was not obviously higher than that in the disease control (144.8 $\pm$ 10.04ng/ml,  $P > 0.05$ ). Importantly, the level of CSF sCD146 was prominently decreased after glucocorticoid treatment compared with that before NPSLE treatment (32.54 $\pm$ 4.11 vs 19.12 $\pm$ 1.60 ng/ml  $P < 0.001$ ). Moreover, abnormally increased sCD146 in the CSF of NPSLE patients correlated with ESR, C3, C4 from sera. Importantly, the level of CSF sCD146 was correlated with the level of inflammatory factors (MCP, IL-23 and MMP-9) in the CSF. **[Conclusion]** We found significantly higher levels of sCD146 in CSF of NPSLE patients compared with other neuropsychiatric diseases. Moreover, some correlations were observed between the CSF sCD146 levels and measures of disease activity in NPSLE patients. Therefore, CSF level of sCD146 may provide a potential marker for NPSLE patients.

### ICW-B9-6

#### Characterization of Phenotype and Function of Dectin-1 on Monocyte-Derived Dendritic Cells in Patients with Systemic Lupus Erythematosus

Ky Lam, D Luk, Y Lo, Cs Lau, My Mok

Department of Medicine, Queen Mary Hospital, The University of Hong Kong

Conflict of interest: None

**Background:** Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease that is characterized by dysregulated innate and adaptive immunity. Dectin-1 is a c-type lectin receptor that is predominantly expressed on innate immune cells such as monocytes and dendritic cells (DCs) and is involved in fungal immunity. **Objectives:** To examine the phenotype and function of dectin-1 in monocytes and DCs in SLE patients **Methods:** Expression of dectin-1 and monocytic function of reactive oxygen species (ROS) on SLE and control monocytes were examined by flow cytometry. Cytokine production including IL-1 $\beta$ , IL-6, IL-10 and IL-12 were measured by multiplex bead immunoassay. **Results:** Significantly lower dectin-1 level was expressed on CD14<sup>+</sup> monocytes in SLE patients compared to healthy controls, and was found to correlate inversely with SLE disease activity index and anti-dsDNA antibody level. These lupus monocytes also produced significantly higher ROS level. However, treatment with active and inactive SLE serum did not change levels of dectin-1 expression. Expression of dectin-1 was not different between patients and controls after differentiation into DCs. However, these SLE monocyte-derived DCs showed enhanced phosphor-syk signaling and produced higher level of IL-1 $\beta$  upon dectin-1 stimulation.

**Conclusions:** Dectin-1 is phenotypically and functionally abnormal on SLE monocytes and monocyte-derived DCs suggesting that this c-type lectin receptor may be involved in the pathogenesis of SLE.

## Workshop

### W1-1

#### **Kinetics of clinical efficacy of Certolizumab pegol (C-OPERA study)**

Tatsuya Atsumi<sup>1</sup>, Kazuhiko Yamamoto<sup>2</sup>, Tsutomu Takeuchi<sup>3</sup>, Hisashi Yamanaka<sup>4</sup>, Yoshiya Tanaka<sup>5</sup>, Naoki Ishiguro<sup>6</sup>, Katsumi Eguchi<sup>7</sup>, Toshiharu Shoji<sup>8</sup>, Nobuyuki Miyasaka<sup>9</sup>, Takao Koike<sup>10</sup>

<sup>1</sup>Graduate School of Medicine Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, <sup>2</sup>Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, <sup>3</sup>Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, <sup>4</sup>Institute of Rheumatology, Tokyo Women's Medical University, <sup>5</sup>First Department of Internal Medicine, University of Occupational and Environmental Health, <sup>6</sup>Department of Orthopedic Surgery, Nagoya University Graduate School and Faculty of Medicine, <sup>7</sup>Sasebo City General Hospital, <sup>8</sup>Department of Clinical Research and Development, UCB Japan Co. Ltd., <sup>9</sup>Tokyo Medical and Dental University, <sup>10</sup>NTT Sapporo Medical Center

Conflict of interest: Yes

**Objective** To evaluate kinetics of clinical efficacy between certolizumab pegol (CZP)+MTX and MTX monotherapy in early RA (ERA)

**Methods** MTX naïve ERA patients fulfilling the 2010 ACR/EULAR Classification Criteria with poor prognostic factors: high-positive anti-CCP (>3xULN), and either positive rheumatoid factor or erosion on radiographs were enrolled in C-OPERA study. Patients were randomized 1:1 to either CZP200mg+MTX with loading dose or placebo (PBO)+MTX with MTX escalated to 16mg by Week (Wk) 8 unless safety issues and tolerability precluded further dose increase. Clinical efficacy were measured at baseline, Week 1, 2, 4, 6, 8 and onwards at every 4 weeks up to Wk 52. **Results:** CZP+MTX group (n=159) showed higher ACR20/50/70 responses compared to PBO+MTX group (n=157). CZP+MTX had significantly greater improvements in all ACR core components throughout the study period from Wk1. DAS28 (ESR) and HAQ remission rates were higher in CZP+MTX group compared to PBO+MTX group at all time points (p<0.01 and P<0.05, respectively). SDAI and Boolean remission rates were also higher at majority time points. **Conclusions:** CZP+MTX showed rapid and sustained improvements in signs and symptoms of RA compared to MTX monotherapy in ERA who were MTX-naïve with poor prognostic factors.

### W1-2

#### **Efficacy and safety of Certolizumab pegol (CZP) by MTX dose (C-OPERA study) in early RA patients**

Yoshiya Tanaka<sup>1</sup>, Tatsuya Atsumi<sup>2</sup>, Kazuhiko Yamamoto<sup>3</sup>, Tsutomu Takeuchi<sup>4</sup>, Hisashi Yamanaka<sup>5</sup>, Naoki Ishiguro<sup>6</sup>, Katsumi Eguchi<sup>7</sup>, Toshiharu Shoji<sup>8</sup>, Nobuyuki Miyasaka<sup>9</sup>, Takao Koike<sup>10</sup>

<sup>1</sup>First Department of Internal Medicine, University of Occupational and Environmental Health, <sup>2</sup>Graduate School of Medicine Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, <sup>3</sup>Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, <sup>4</sup>Medicine, Keio University School of Medicine, <sup>5</sup>Institute of Rheumatology, Tokyo Women's Medical University, <sup>6</sup>Department of Orthopedic Surgery, Nagoya University Graduate School and Faculty of Medicine, <sup>7</sup>Sasebo City General Hospital, <sup>8</sup>Department of Clinical Research and Development, UCB Japan Co. Ltd., <sup>9</sup>Tokyo Medical and Dental University, <sup>10</sup>NTT Sapporo Medical Center

Conflict of interest: Yes

**Objective:** To evaluate efficacy and safety of CZP+MTX by MTX dose in early RA (ERA) patients **Methods** MTX naïve ERA fulfilling 2010 ACR/EULAR Classification Criteria with poor prognostic factors: high-positive anti-CCP (>3xULN), and either positive rheumatoid factor or erosion on radiographs were enrolled in C-OPERA. Patients were randomized 1:1 to either CZP200mg/Wk+MTX with loading dose or placebo (PBO)+MTX with MTX escalated to 16mg by Week (Wk) 8 unless safety issues and tolerability precluded further dose increase. MTX dose was recorded at every week over 52 Wks. Safety and efficacy of CZP+MTX or MTX were analyzed by -3 different MTX dose subgroups (mean 0-8, 8-12, 12-16mg/Wk). **Results:** MTX dose was plateaued by

Wk 8-9 (the mean dose 12mg/Wk), but over 40% could not be increased to 16mg/Wk during the study. CZP+MTX showed clinical efficacy (DAS28 (ESR) SDAI, and Boolean remission) in all MTX-dose groups except for Boolean remission in low dose MTX group. However, the rate of some adverse events were dependent on MTX dose. In particular, the rate of hepatic disorders was 2 or 3 times higher in higher dose MTX group than in the lower dose MTX group. **Conclusions:** Efficacy of CZP+MTX was shown in all MTX dose groups in ERA, but some adverse events (hepatic disorder) was dose-dependent.

### W1-3

#### **Efficacy and safety of MTX at the highest tolerable dose in early RA (C-OPERA)**

Yoshiya Tanaka<sup>1</sup>, Tatsuya Atsumi<sup>2</sup>, Kazuhiko Yamamoto<sup>3</sup>, Tsutomu Takeuchi<sup>4</sup>, Hisashi Yamanaka<sup>5</sup>, Naoki Ishiguro<sup>6</sup>, Katsumi Eguchi<sup>7</sup>, Toshiharu Shoji<sup>8</sup>, Nobuyuki Miyasaka<sup>9</sup>, Takao Koike<sup>10</sup>

<sup>1</sup>First Department of Internal Medicine, University of Occupational and Environmental Health, <sup>2</sup>Graduate School of Medicine Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, <sup>3</sup>Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, <sup>4</sup>Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, <sup>5</sup>Institute of Rheumatology, Tokyo Women's Medical University, <sup>6</sup>Department of Orthopedic Surgery, Nagoya University Graduate School and Faculty of Medicine, <sup>7</sup>Sasebo City General Hospital, <sup>8</sup>Department of Clinical Research and Development, UCB Japan Co. Ltd., <sup>9</sup>Tokyo Medical and Dental University, <sup>10</sup>NTT Sapporo Medical Center

Conflict of interest: Yes

[Objectives] To analyze the efficacy and safety of high dose methotrexate (MTX) in early RA in C-OPERA study [Methods] C-OPERA aimed to study efficacy and safety of certolizumab pegol+MTX in MTX-naïve ERA patients who had poor prognostic factors. C-OPERA placebo+MTX arm was analyzed in this report. MTX was started at 8 mg/week (wk) and dose escalation was conducted up to 16 mg/wk at Wk8 only based on tolerability. Efficacy of MTX was compared between subgroups stratified by mean MTX dose throughout the study period (0-8, 8-12, 12-16 mg/wk) and baseline parameters. Incidence of adverse event (AE) was assessed by MTX dose at the onset. [Results] Overall, the MTX dose peaked at 8-9 wks, with mean dose throughout the study of 11.6 mg/wk. At Wk52, clinical remission rates were higher in the highest MTX dose group than the lowest (DAS28 remission: 42.9% vs 33.3%), whereas inhibition of joint damage progression (JDP) did not positively associate with MTX dose. Wk52 JDP associated with baseline parameters including CRP, disease activity, and JDP. Higher incidence of gastrointestinal and hepatobiliary disorders were reported in higher MTX doses. [Conclusion] MTX dose positively associated with clinical remissions but not with inhibition of JDP. Incidences of several AEs were MTX dose-dependent.

### W1-4

#### **Clinical efficacy of certolizumab pegol therapy in patients with active rheumatoid arthritis ~A MULTICENTER REGISTRY STUDY~**

Yasuhide Kanayama<sup>1</sup>, Atsushi Kaneko<sup>2</sup>, Nobunori Takahashi<sup>3</sup>, Takefumi Kato<sup>4</sup>, Yuji Hirano<sup>5</sup>, Kenya Terabe<sup>3</sup>, Yosuke Hattori<sup>2</sup>, Yuichiro Yabe<sup>6</sup>, Nobuyuki Asai<sup>3</sup>, Takayoshi Fujibayashi<sup>7</sup>, Tomone Shioura<sup>8</sup>, Tsuyoshi Watanabe<sup>9</sup>, Takayasu Ito<sup>10</sup>, Masatoshi Hayashi<sup>11</sup>, Shinya Hirabara<sup>5</sup>, Kiwamu Saito<sup>12</sup>, Masahiro Hanabayashi<sup>13</sup>, Naoki Ishiguro<sup>3</sup>, Toshihisa Kojima<sup>3</sup>

<sup>1</sup>Department of Orthopedic Surgery and Rheumatology, Toyota Kosei Hospital, Toyota, Japan, <sup>2</sup>Department of Orthopedic Surgery, Nagoya Medical Center, Nagoya, Japan, <sup>3</sup>Department of Orthopedic Surgery and Rheumatology, Nagoya University Graduate School of Medicine, Nagoya, Japan, <sup>4</sup>Department of Orthopedic Surgery, Kato Clinic, Okazaki, Japan, <sup>5</sup>Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan, <sup>6</sup>Department of Rheumatology, Tokyo Shinjuku Medical Center, Tokyo, Japan, <sup>7</sup>Department of Orthopedic Surgery, Konan Kosei Hospital, Konan, Japan, <sup>8</sup>Department of Rheumatology, Shizuoka Kosei Hospital, Shizuoka, Japan, <sup>9</sup>Department of Orthopedic Surgery, Kariya Toyota General Hospital, Kariya, Japan, <sup>10</sup>Department of Orthopedic Surgery, Ito Clinic, Nagoya, Japan, <sup>11</sup>Department of Orthopedic Sur-

gery, Nagano Red Cross Hospital, Nagano, Japan, <sup>12</sup>Department of Orthopedic Surgery and Rheumatology, Saito Clinic, Nagoya, Japan, <sup>13</sup>Department of Orthopedic Surgery, Ichinomiya Municipal Hospital, Ichinomiya, Japan, <sup>14</sup>Department of Orthopedic Surgery, Nagoya Central Hospital, Nagoya, Japan

Conflict of interest: None

[Objectives] To evaluate the clinical efficacy of Certolizumab pegol (CZP) in patients with RA. [Methods] Patients with a diagnosis of RA according to the 2010 ACR/EULAR criteria who had been prescribed CZP from TBCR between April 2013 and April 2014 were enrolled. The final study cohort of 53 patients received continuous CZP therapy more than 24 weeks. We reviewed the methods about the improvement of DAS28-ESR and the rate of remission patients at Week24 by LOCF method. [Results] The group of patients included 13 males and 40 females. The mean age was 60.4±13.9 years old; the disease duration was 9.8±9.8 years and the patients of receiving methotrexate was 42 cases (79%). Clinical findings related to RA were as follows: mean tender and swollen joint count, 5.4±4.4 and 5.5±4.3; patient's and physician's global assessment of disease activity, 50.0±25.9mm and 44.0±20.8mm; CRP, 1.7±1.9 mg/dL; ESR, 42.2±33.6 mm/h. The DAS28 improved from 4.89±1.34 at baseline to 3.66±1.46, 3.55±1.57 and 3.47±1.55 at Week 4, 12 and 24 (p<0.001, p<0.001, p < 0.001) significantly. At Week 4, 12 and 24 the rate of patients who achieved remission were each 26.7%, 30.4%, and 29.8% in DAS criteria. [Conclusion] This study suggested that the new TNF-antagonist therapy of CZP was effective in patients with RA.

### W1-5

#### **Effect of certolizumab pegol on work productivity in patients with early rheumatoid arthritis (C-OPERA study)**

Hisashi Yamanaka<sup>1</sup>, Tatsuya Atsumi<sup>2</sup>, Kazuhiko Yamamoto<sup>3</sup>, Tsutomu Takeuchi<sup>4</sup>, Yoshiya Tanaka<sup>5</sup>, Naoki Ishiguro<sup>6</sup>, Katsumi Eguchi<sup>7</sup>, Toshiharu Shoji<sup>8</sup>, Nobuyuki Miyasaka<sup>9</sup>, Takao Koike<sup>10</sup>

<sup>1</sup>Institute of Rheumatology, Tokyo Women's Medical University, <sup>2</sup>Graduate School of Medicine Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, <sup>3</sup>Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, <sup>4</sup>Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, <sup>5</sup>First Department of Internal Medicine, University of Occupational and Environmental Health, <sup>6</sup>Department of Orthopedic Surgery, Nagoya University Graduate School and Faculty of Medicine, <sup>7</sup>Sasebo City General Hospital, <sup>8</sup>Department of Clinical Research and Development, UCB Japan Co. Ltd., <sup>9</sup>Tokyo Medical and Dental University, <sup>10</sup>NTT Sapporo Medical Center

Conflict of interest: Yes

[Objectives] To examine effectiveness of certolizumab pegol on work productivity in early rheumatoid arthritis patients. [Methods] MTX naïve patients with ≤12 months of persistent arthritis, fulfilling the 2010 ACR/EULAR Classification Criteria with poor prognostic factors were enrolled in C-OPERA study. Patients were randomized to either CZP+MTX or placebo (PBO)+MTX. Work productivity was evaluated by questionnaire at baseline, week (W)24 and W52. [Results] Patients[BMI] negatively impacted by arthritis on job status were 23.7% at baseline and 24.0% at W52 in PBO+MTX, and 23.2% and 16.0%, respectively, in CZP+MTX. Among patients who stayed at home, 34.4% at baseline and 28.1% at W52 in PBO+MTX and 27.3% and 2.9%, respectively, in CZP+MTX experienced days could not work throughout a day, and 71.9% at baseline and 37.5% at W52 in PBO+MTX and 66.7% and 20.6%, respectively, in CZP+MTX should shorten their working time. Patients needed someone's assistance for daily activities were 29.9% at baseline and 22.4% at W52 in PBO+MTX vs 31.2% and 13.3% in CZP+MTX. [Conclusion] CZP showed tendency to ameliorate negative impact of arthritis on work status and reduced necessity for assistance. Although interpretations are limited, CZP seems to improve work productivity in patients with ERA.

## W1-6

### Sustainable Efficacy and Safety of Certolizumab Pegol over 4 years in Patients with Rheumatoid Arthritis (J-RAPID / HIKARI OLE studies)

Hisashi Yamanaka<sup>1</sup>, Kazuhiko Yamamoto<sup>2</sup>, Tsutomu Takeuchi<sup>3</sup>, Yoshiya Tanaka<sup>4</sup>, Naoki Ishiguro<sup>5</sup>, Katsumi Eguchi<sup>6</sup>, Toshiharu Shoji<sup>7</sup>, Nobuyuki Miyasaka<sup>8</sup>, Takao Koike<sup>9</sup>

<sup>1</sup>Institute of Rheumatology, Tokyo Women's Medical University, <sup>2</sup>Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, <sup>3</sup>Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, <sup>4</sup>First Department of Internal Medicine, University of Occupational and Environmental Health, <sup>5</sup>Department of Orthopedic Surgery, Nagoya University Graduate School and Faculty of Medicine, <sup>6</sup>Sasebo City General Hospital, <sup>7</sup>Department of Clinical Research and Development, UCB Japan Co. Ltd., <sup>8</sup>Tokyo Medical and Dental University, <sup>9</sup>NTT Sapporo Medical Center

Conflict of interest: Yes

[Objectives] To examine the long-term safety, efficacy and retention rate of certolizumab pegol (CZP) therapy. [Methods] In J-RAPID (with MTX) and HIKARI (without MTX) patients (pts) who completed the double-blind trials (completer) and pts who withdrew at Wk16 per protocol (EE) 1 were eligible to enter the respective open-label extensions (OLEs). Pts were treated with CZP 200 mg Q2W or 400 mg Q4W. [Results] 285 pts in J-RAPID and 208 pts in HIKARI enrolled the respective OLEs. Overall, 97.2% and 93.8% of pts experienced adverse events (AEs), and 23.9% and 36.5% experienced serious AEs. One and 2 pts resulted in death, respectively. No new safety signals were observed. Improvements in DAS28 at Wk206 from the baseline were observed (J-RAPID: 6.23→2.82 in completer and 6.52→3.53 in EE, HIKARI: 6.11→3.24 in completers and 6.27→3.67 in EE). Retention rates at Wk208 were 66.3% in J-RAPID and 57.7% in HIKARI. [Conclusion] CZP with/without MTX provided a favorable efficacy and safety profile with similar retention rates over 4 year-treatment in RA. No new safety signals were identified in these OLE studies.

## W2-1

### The effectiveness and safety of Certolizumab pegol in the multiple center study

Yuho Kadono<sup>1</sup>, Tetsuro Yasui<sup>1</sup>, Jinju Nishino<sup>1</sup>, Sakae Tanaka<sup>1</sup>, Keita Nishimura<sup>2</sup>, Hajime Kono<sup>3</sup>, Toshihiro Matsui<sup>4</sup>, Kanako Iwata<sup>5</sup>, Shigeto Tohma<sup>5</sup>, Yuichi Nagase<sup>6</sup>, Takuji Nishikawa<sup>6</sup>, Yasuhiko Koizumi<sup>7</sup>, Takeshi Matsumoto<sup>7</sup>, Ichiro Nakamura<sup>8</sup>, Takuo Juji<sup>8</sup>, Katsumi Ito<sup>8</sup>

<sup>1</sup>Orthopaedic Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, <sup>2</sup>Department of Orthopaedic Surgery, School of Medicine, Teikyo University, Tokyo, Japan, <sup>3</sup>Department of Internal Medicine, School of Medicine, Teikyo University, Tokyo, Japan, <sup>4</sup>Department of Rheumatology, National Hospital Organization Sagamihara Hospital, Sagamihara, Japan, <sup>5</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, National Hospital Organization, Sagamihara Hospital, Sagamihara, Japan, <sup>6</sup>Department of Rheumatology, Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan, <sup>7</sup>Department of Orthopedic Surgery, Yokohama Rosai Hospital, Yokohama, Japan, <sup>8</sup>Department of Rheumatology, Japan Community Health Care Organization Yugawara Hospital, Yugawara, Japan

Conflict of interest: Yes

[Objectives] To clarify the effectiveness and safety of CZP for RA patients in multiple centers. [Methods] The information listed below were collected: age, sex, disease duration, drugs (MTX, steroid and biologics), tender joint count, swelling joint count, patient global assessment, doctor global assessment, CRP, ESR and adverse events before and 4, 12, and 24 weeks after CZP administration. [Results] Forty-nine cases (average age 60.0 years old, and disease duration 10.4 years) were registered. Thirty-two cases used MTX (average 8.1 mg/week), and 29 used steroid (average 2.7 mg/day). The biologics naïve was 16 cases, and the second or more was 33 cases. At the time of administration, average DAS28-ESR was 3.12, SDAI 20.86, CDAI 18.60. Symptom improvement was seen after 4 weeks, and decreased to 2.27, 10.21, 9.93, respectively ( $p < 0.01$ ) after 24 weeks. Herpes zoster and bronchitis were seen in each case. The continuation rate in 24 weeks was 61.2% when we count-

ed in 17 cases of insufficient effectiveness. A continuation rate in cases with the second or more was lower than the naïve cases. [Conclusion] The clinical effect of CZP was seen in 4 weeks. Adverse events were seen in a few. When we uses as a second or more, about half canceled by 24 weeks because of insufficient effect.

## W2-2

### Efficacy of the initial treatment with certolizumab pegol for rheumatoid arthritis in multicenter study TBCR

Yosuke Hattori<sup>1</sup>, Atsushi Kaneko<sup>1</sup>, Naoki Fukaya<sup>2</sup>, Takefumi Kato<sup>3</sup>, Takayasu Ito<sup>4</sup>, Hideki Takagi<sup>5</sup>, Daihei Kida<sup>1</sup>, Yasuhide Kanayama<sup>6</sup>, Yuji Hirano<sup>7</sup>, Tsuyoshi Watanabe<sup>2</sup>, Takayoshi Fujibayashi<sup>8</sup>, Nobunori Takahashi<sup>10</sup>, Koji Funahashi<sup>10</sup>, Kiwamu Saito<sup>9</sup>, Hiroyasu Kanda<sup>1</sup>, Toshihisa Kojima<sup>10</sup>, Naoki Ishiguro<sup>10</sup>

<sup>1</sup>Department of Orthopaedic Surgery and Rheumatology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Kariya Toyota General Hospital, <sup>3</sup>Kato Clinic, <sup>4</sup>Ito Seikeigeka, <sup>5</sup>Department of Orthopaedic Surgery, Nagoya Central Hospital, <sup>6</sup>Department of Orthopaedic Surgery, Toyota Kosei Hospital, <sup>7</sup>Department of Rheumatology, Toyohashi Municipal Hospital, <sup>8</sup>Department of Orthopaedic Surgery, Konan Kosei Hospital, <sup>9</sup>Saito Clinic, <sup>10</sup>Department of Orthopaedic Surgery, Nagoya University Graduate School of Medicine

Conflict of interest: Yes

[Objectives] We evaluate the efficacy of the loading dosage with certolizumab pegol (CZP) for rheumatoid arthritis (RA). [Methods] 34 patients with RA who underwent CZP treatment and 137 patients with RA who underwent adalimumab (ADA) treatment were enrolled in this study. Those patients had not received previous biologic treatment. [Results] The rate of improvement (mean·median (IQR)) in DAS28-CRP at 4 weeks is 54%·50 (30-73)% in CZP group and 36%·34 (16-55)% in ADA group. The rate of improvement in CRP levels at 4 weeks is 65%·75 (54-91)% in CZP group and 32%·75 (35-90)% in ADA group. The rate of improvement in MMP-3 levels at 4 weeks is 31%·35 (16-54)% in CZP group and 18%·34 (5.0-73)% in ADA group, respectively. [Conclusion] In this study, the response of CZP treatment at 4 weeks is equal to ADA or better, and there were few ineffectiveness cases. We suggested that the loading dosage developed sure efficacy of the initial treatment with CZP for RA.

## W2-3

### The efficacy of certolizumab pegol with pretreatment of other biologic agents or not for patients of rheumatoid arthritis from multicenter study TBC

Nobuyuki Asai<sup>1</sup>, Kenya Terabe<sup>1</sup>, Yasuhide Kanayama<sup>2</sup>, Atsushi Kaneko<sup>3</sup>, Yuji Hirano<sup>4</sup>, Tomone Shioura<sup>5</sup>, Takayoshi Fujibayashi<sup>6</sup>, Nobunori Takahashi<sup>1</sup>, Koji Funahashi<sup>1</sup>, Toshihisa Kojima<sup>1</sup>, Naoki Ishiguro<sup>1</sup>

<sup>1</sup>Nagoya University Graduate School of Medicine, Nagoya, Japan, <sup>2</sup>Toyota Kosei Hospital, <sup>3</sup>Nagoya Medical Center, <sup>4</sup>Toyohashi Municipal Hospital, <sup>5</sup>Shizuoka kosei Hospital, <sup>6</sup>Konan Kosei Hospital

Conflict of interest: None

We evaluated efficacy of certolizumab pegol (CZP) with pretreatment of other biologic agents or not for patients of rheumatoid arthritis. These results are derived from multicenter study from TBC. Efficacy was evaluated based on DAS28-ESR, as well as retention rate, and safety at 24 weeks in 53 RA patients. In baseline characteristic, proportions of combined MTX were different in two groups (naïve: 88% switch: 63%). The retention rate at 24 weeks period was 81.8% in naïve group, 42.1% in switch group. Average of DAS28-ESR improved 4.81±1.35 to 2.77±1.05 in naïve group, 4.86±1.25 to 4.52±1.60 in switch group after 24 weeks later. 100 patient-years of adverse events were 28.7 in naïve group, 35.5 in switch group. In switch group comparing pre administered biologics between anti TNF- $\alpha$  inhibitors (n=10) and others (n=9), The retention rate of anti TNF- $\alpha$  group was 60.0% in anti TNF- $\alpha$  group, those was 28.5% in others group.

## W2-4

### Prediction of certolizumab pegol continuity in clinical practice focused on rheumatoid arthritis disease activity at four weeks after its initial administration

Masaki Katayama, Hirotaka Itoh, Sohei Funakoshi

Department of Rheumatology and Clinical Immunology, Osaka Red Cross Hospital, Osaka, Japan

Conflict of interest: None

**[Objectives]** Some rheumatoid arthritis (RA) patients achieve clinical remission promptly after Certolizumab pegol (CZP) is administered because of its induction dose, others early discontinue it because it is primarily not effective. We now identify the relationship between RA disease activity at four weeks after CZP initial administration and its continuity. **[Methods]** We analyze 23 patients retrospectively who received CZP and were observed from August 2013 to October 2014. We define the group as “responsive group” in which low disease activity or remission in DAS28-CRP was achieved at four weeks after CZP initial administration, and “nonresponsive group” high or moderate disease activity. We compare the backgrounds and CZP continuity. **[Results]** 14 patients are included into “responsive group” and 9 “nonresponsive group”. RA disease activity of CZP initial administration is lower in responsive group. Age, sex, MTX dose, RA disease duration and so on are not statistically different. In logrank test and Cox proportional hazard test, CZP continuity until twelve months is better in responsive group. **[Conclusions]** In clinical practice, if RA disease activity at four weeks after CZP initial administration is not remission or low disease activity, CZP will be often discontinued.

## W2-5

### The impact of chronic kidney disease (CKD) on drug survival rate (DSR) in Rheumatoid arthritis (RA) patients who received certolizumab pegol (CZP)

Naoki Sawa, Eiko Hasegawa, Rikako Hiramatsu, Aya Imafuku, Masahiro Kawada, Junichi Hoshino, Tatsuya Suwabe, Yoshifumi Ubara, Kenmei Takaichi

Departments of Nephrology, Toranomon Hospital, Tokyo, Japan

Conflict of interest: None

**[Objectives]** To analyze the impact of CKD on DSR in RA patients who received CZP. **[Methods]** A retrospective study was performed to analyze the risk factors which affected DSR of CZP. The primary endpoint was 6 month DSR after starting CZP. DSR analyses were performed using the log-rank test and Cox regression models. Covariates for our multivariate model were selected by using a likelihood ratio test. **[Results]** In 54 RA patients treated with CZP, 31 patients had CKD and 23 patients had normal renal function (non CKD). 6 month DSR was significant higher in the non CKD group than the CKD group (90.6% vs 61.2%;  $p=0.02$ ). Other factors that effect on DSR of CZP were positive anti CCP antibody, Age  $\geq 75$  year and MTX dose  $\geq 6$  mg/week. According to the Cox proportional hazards model employing only one covariates, MTX dose  $\geq 6$  mg/week was associated with a 68% reduction of 6month DSR of CZP (versus MTX dose  $< 6$  mg/week; HR=0.21 (0.061-0.71);  $p=0.01$ ) **[Conclusion]** We found that CKD was not significant risk factor of DSR of CZP in RA patients.

## W2-6

### The efficacy and retention rate of biologics in our hospital; 2015 edition

Junichi Fujisawa<sup>1</sup>, Naoki Kondo<sup>2</sup>, Naoko Kudo<sup>2</sup>, Naoto Endo<sup>2</sup>, Katsumitsu Arai<sup>3</sup>, Takahiro Netsu<sup>4</sup>, Takeshi Kuroda<sup>5</sup>, Yoko Wada<sup>5</sup>, Takeshi Nakatsue<sup>5</sup>  
<sup>1</sup>Carrier Support Center for Resident, Niigata University Medical and Dental Hospital, Niigata, Japan, <sup>2</sup>Division of Orthopedic Surgery, Department of Regenerative and Transplant Medicine, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, <sup>3</sup>Division of Orthopedic Surgery, Niigata Prefectural Central Hospital, Niigata, Japan, <sup>4</sup>Division of Rheumatology, Nagaoka Red Cross Hospital, Niigata, Japan, <sup>5</sup>Department of Medicine II, Niigata University Medical School, Niigata, Japan

Conflict of interest: None

**[Objectives]** To examine the efficacy and retention rate of biologics in our hospital. **[Methods]** 529 patients who started to treat biologics between May, 2001 and August, 2014, were included in this study. The average age was 56.6. The average follow-up period was about 2.5-year. They were subdivided as follows; Infliximab (IFX) 64, Etanercept (ETN) 73, ETN+Methotrexate (MTX) 139, Tocilizumab (TCZ) 140, Adalimumab (ADA) 59, Abatacept (ABA) 21, Golimumab (GLM) 19 and Certolizumab pegol (CZP) 14. DAS28 (3)-CRP values on introduction and 6 month after were compared. In addition, Kaplan-Meier survival rates were plotted to determine retention rate for each group. **[Results]** DAS28 (3)-CRP value on introduction was 4.17 in IFX, 3.82 in ETN, 3.82 in ETN+MTX, 3.65 in TCZ, 3.21 in ADA, 3.40 in ABA, 3.37 in GLM and 3.03 in CZP group, respectively. Then 6 months after, each value was 2.74, 2.51, 2.29, 2.13, 2.16, 2.28, 2.35 and 2.42. The retention rate 1 year after was 70.5 in IFX, 74.0 in ETN, 81.7 in ETN+MTX, 77.5 in TCZ, 65.5 in ADA, 69.8 in ABA, 40.1 in GLM and 76.2 in CZP group, respectively. The retention rate 2 years was 59.0, 66.9, 75.3, 70.6, 56.5, 69.2, 40.1 and 76.2, respectively. **[Conclusion]** These findings suggest that each group showed almost the same efficacy in DAS28 (3)-CRP

## W3-1

### Clinical characteristics in patients with giant cell arthritis in our institution

Natsuki Shima, Takao Nagashima, Masahiro Iwamoto, Seiji Minota  
Division of Rheumatology and Clinical Immunology, Department of Medicine, Jichi Medical University, Tochigi, Japan

Conflict of interest: None

**[Objectives]** To investigate clinical characteristics and treatment response in patients with giant cell arthritis (GCA) in our institution. **[Methods]** Patients who were diagnosed with GCA between January 1995 and October 2014 were retrospectively reviewed. **[Results]** Nineteen patients with the mean age of 72 (range 62-83) were found to have GCA. Twelve out of 19 were women. Three patients had concomitant polymyalgia rheumatica (PMR). Histopathological evidence of vasculitis by temporal artery biopsy was demonstrated in 12. Clinical symptoms are the followings: systemic symptoms (fever, malaise, anorexia, or weight loss) in 12; headache in 17; jaw claudication in 7; and scalp tenderness in 5. No patient had visual symptoms. Extracranial artery involvement was detected in 9. Ninety percent of the patients had erythrocyte sedimentation rate above 50 mm/h. All patients were treated with oral prednisolone (PSL). Eight patients required moderate- to high-dose PSL (equal or more than 0.6 mg/kg/day), while 11 patients required relatively low-dose PSL (less than 0.6 mg/kg/day). **[Conclusion]** The incidence of concomitant PMR was low in patients with GCA in our institution. Lower dose PSL might be sufficient to suppress arterial inflammation in GCA.

## W3-2

### Clinical study of giant cell arteritis in our department

Eiichi Suematsu, Tomoya Miyamura, Masataka Nakamura, Makiko Higuchi, Shoko Kodama, Yu Kaku, Soichiro Takahama, Rumi Minami, Masahiro Yamamoto  
Department of Internal Medicine and Rheumatology, National Hospital Organization Kyushu Medical Center

Conflict of interest: None

**[Objectives]** To investigate the clinical and laboratory features of giant cell arteritis (GCA). **[Methods]** Twenty two patients (6 male and 16 female) were included this study. Diagnosis of GCA was carried out based on ACR1990 classification criteria. **[Results]** Mean age was 66.6 year old. Mean level of serum CRP was 8.94mg/dl. GCA was divided to 3 types, ie classical temporal arteritis type (9 cases), large vessel type which affected aorta and its major branches without temporal artery (11 cases), and generalized type which affected both temporal artery and large vessels (2 cases). Swelling and tender of temporal arteries were recognized in temporal arteritis type and generalized type, 9 of them revealed the histopathological findings of arteritis including giant cells in the biopsy specimens. Eight cases were positive for antiphospholipid an-



tibodies (7 for anticardiolipin antibody IgG, 7 for anticardiolipin  $\beta_2$ GPI antibody, 0 for lupus anticoagulant). [Conclusion] Our study demonstrates that high prevalence of antiphospholipid antibodies in GCA cases, although obvious thrombotic events related to GCA were not observed.

### W3-3

#### **A case study, which is useful to diagnose of Temporal Arteritis occurred Polymyalgia Rheumatica by head contrast 3D Computed Tomography**

Toshio Kawamoto<sup>1</sup>, Kenjiro Yamanaka<sup>1</sup>, Souichiro Nakano<sup>2</sup>, Satoshi Suzuki<sup>2</sup>, Ran Matsudaira<sup>1</sup>, Yoshinori Kanai<sup>1</sup>, Yoshinari Takasaki<sup>2</sup>

<sup>1</sup>Kyoundo Hospital, <sup>2</sup>Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine

Conflict of interest: None

**Purpose:** We experienced a case with cryptogenic headache, myalgia and arthralgia, which could be diagnosed by head contrast 3D Computed Tomography (CT). We report the case with consideration with literature. **Present Illness:** 75 years male was diagnosed Polymyalgia Rheumatica (PMR) in another hospital in 2006. He was diagnosed to seronegative RA with polyarthritis July in 2012, and ameliorated using prednisolone (PSL) 4mg and salazosulfapyridine. He was hospitalized because of myalgia, arthralgia and headache with pain of eye and CRP raised and medicated PSL30mg, symptom remained. **Progression after hospitalization:** Though the cause did not become clear by MRI and PET-CT, stoppage of right temporal arteritis was recognized by head contrast 3D CT. We diagnosed Temporal Arteritis, and administered steroid semi-pulse therapy and PSL50mg. So symptom and stoppage of right temporal arteritis improved. After that PSL was gradually reduced to 30mg, because CRP raised we administered tacrolimus with PSL. **Consideration:** Recently it is noteworthy that angitis is indicated by PET-CT. In this case he was indicated contraction of temporal artery by head contrast 3D CT which was not indicated by MRI and PET-CT. We report the method of diagnosis of giant cell arthritis with PMR with literature.

### W3-4

#### **Initial treatment responses for patients with Takayasu arteritis and long-term treatment outcomes**

Yukihide Ono<sup>1</sup>, Yukiko Tokuda<sup>1</sup>, Yuri Sadanaga<sup>1</sup>, Satoko Tashiro<sup>1</sup>, Rie Suematsu<sup>1</sup>, Nobuyuki Ono<sup>1</sup>, Syuichi Koarada<sup>1</sup>, Akihide Ohta<sup>2</sup>, Yoshifumi Tada<sup>1</sup>

<sup>1</sup>Department of Rheumatology Faculty of Medicine, Saga University, <sup>2</sup>Department of Adult and Gerontological Nursing, Saga University

Conflict of interest: None

**Objectives:** We investigated the relationship initial treatment responses with Takayasu arteritis (TA) and long-term outcomes. **Methods:** We collected patients' data through clinical records between 1994 and 2014. **Results:** We found 14 TA patients (13 female). The mean onset ages of TA was 29 years old. The follow-up time was 7.2 years. As initial treatment, all patients were treated with corticosteroid (CS) alone. The mean initial dose of PSL was 32.1 mg/day. During their follow-ups, 3 could stop CS, 8 needed immunosuppressants (IS: 6 MTX, 2 CyA, 1 TAC), and 2 were treated with biologics (1 IFX, 1 GLM). Among 6 patients treated with CS alone, the final dose of PSL was 2.2mg/day and 2 could stop CS. Among 8 patients with additional IS, the final dose of PSL was 7.4mg/day, and one with biologic could stop CS. Among 9 patients whose CRP values were normalized one month after initial treatments, the mean final dose of PSL was 3.2mg/day. Two could stop CS, and 4 needed IS. Among 5 patients whose CRP values were not normalized after one month, the final dose of CS were 12.0mg/day. One could stop CS, and 4 needed IS. **Conclusions:** Among patients whose CRP values were not normalized after initial treatment, they were treated with more CS and IS. They may be treated with biologics earlier.

### W3-5

#### **The clinical features of Takayasu's arteritis in our hospital (52 cases)**

Takumi Nagamoto, Rintaro Saito, Yuri Nakamura, Yoshie Gon, Hisayo Horiuchi, Hirotaka Yamada, Kenta Misaki, Toshihiko Yokota

Department of Endocrinology and Rheumatology Kurashiki Central Hospital

Conflict of interest: None

**[Objectives]** To reveal Clinical findings and prognosis of Takayasu's arteritis (TA). **[Methods]** From 2000 to 2014, 52 TA patients (female 41, male 11) visited to our hospital were enrolled and analyzed the clinical data retrospectively from medical records. **[Results]** The onset age was 28.8 $\pm$ 1.4 years old and the median time to the diagnosis of TA was 3months. The observation period was 176.7 $\pm$ 17.1 months. Patients were classified into as follows; type I 12, type Iia 5, type Iib 9, type III 1, type IV 1, and type V 21 cases. The stenotic lesions were found in 39 cases, and 37 were found at the first visit. Aneurysm was found in 8 cases, 1 of them was bursted. At the diagnosis, fever was found in 15 cases, claudication or pulse deficit was in 18 cases. AR and cerebral infarction (CI) were revealed in 12 and 3 cases. 2 AR and 2 CI cases were observed after treatment. Revascularization or valve replacement was performed in 13 cases. Combination therapy with immunosuppressants and glucocorticoids were administered in 12 cases and the biologic agents were needed in 3 cases. 4 cases were died (infection: 2, CI: 1, myocardial infarction: 1). **[Conclusion]** In this analysis, stenotic lesion, ischemia and AR were common in early TA, it is necessary to diagnose TA earlier by auscultation and intensive imaging tools.

### W3-6

#### **Current status and new treatment strategy of Takayasu arteritis (TAK) and Giant cell arteritis (GCA) based on the latest case series study**

Takahiko Kurasawa, Katsuya Suzuki, Yuichiro Ota, Tsutomu Takeuchi  
Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Conflict of interest: None

**[Objectives]** Aim of this study is to reveal current status and design new treatment strategy of large vessel vasculitis (LVV). **[Methods]** All cases referred to Rheumatology service at Keio University Hospital from April 2008 until September 2014. Clinical information was collected from medical chart and statistically analyzed. **[Results]** This study enrolled 140 primary vasculitis cases. Classified by vessel size, small was 63, medium was 11, and large was 66 (TAK: 52, GCA: 14) cases. Female was 86.5% of 52 TAK and 64.3% of 14 GCA. Average age at the time of TAK diagnosis was 34.6 $\pm$ 16.8 years old, and GCA was 73.2 $\pm$ 7.8. Six TAK were accompanied with inflammatory bowel diseases. In GCA, polymyalgia rheumatica complication was 35.7% and high diabetes mellitus incidence (64.3%) was observed. In treatment, glucocorticoids (GCs) were used in 76.9% of TAK and all GCA. Rates of concomitant use with immunosuppressant (IS) were 25%(TAK) and 35.7%(GCA). Seven TAK and 1 GCA had history of biologics therapy. IS and biologics use contributed to significant reduction of GCs dose in TAK in the last decade. **[Conclusion]** Although GCs was effective in LLV, long-term GCs administration and its side effects were still problem. New treatment strategy with a view to long-term outcome is suggested.

### W4-1

#### **Clinical Findings of ANCA Associated Vasculitis that Develop with Alveolar Hemorrhage as the Initial Symptom**

Kentaro Isoda, Kenichiro Hata, Katsuhiko Oda  
Department of Rheumatology, Internal Medicine, Yodogawa Christian Hospital, Osaka, Japan

Conflict of interest: None

**[Objectives]** The aim of this study is to investigate clinical findings of ANCA associated vasculitis (AAV) that develop with alveolar hemorrhage as the initial symptom. **[Methods]** This study comprised AAV patients admitted to Yodogawa Christian Hospital from June 2012 to September 2014. This study excluded the patients that AAV re-exacerbated and/or treated before admission to our hospital. We investigated clinical characteristics, therapy, outcome and re-exacerbation of AAV patients that developed with alveolar hemorrhage. **[Results]** Of the 20 patients, 8

(6 were microscopic polyangiitis and 2 allergic granulomatosis-angitis/Churg-Strauss syndrome) developed AAV with alveolar hemorrhage as the initial symptom. Of the 8 patients, 4 were complicated with hemoptysis, 4 with acute renal dysfunction, and 4 with interstitial pneumonia. All patients with alveolar hemorrhage as the initial symptom were treated with high dose corticosteroid (mean prednisolone 0.99 mg/kg/day), 5 with intravenous cyclophosphamide, 2 with plasma exchange. After initial treatment, only 1 patient died, and 2 re-exacerbated. [Conclusion] Although alveolar hemorrhage is a fatal complication of AAV, aggressive initial therapy may improve the prognosis.

#### W4-2

##### **Takayasu arteritis diagnosed during the course of pulmonary hypertension: two case reports**

Takeshi Zoshima, Kazunori Yamada, Shigeto Horita, Hiromi Nuka, Satoshi Hara, Kiyooki Ito, Motohiko Aizu, Hiroshi Fujii, Mitsuhiro Kawano

Division of Rheumatology, Kanazawa University Hospital

Conflict of interest: None

Case 1: Forty nine year old woman presented 3 month history of fever, dyspnea on exertion, and edema of extremities. Pulmonary hypertension (PH) was diagnosed by right heart catheterization (RHC) (mPAP 34 mmHg). During the course, she was detected serum CRP elevation, and enhanced wall thickness and stenosis of bilateral pulmonary arteries (PA) by MRI, and diagnosed Takayasu arteritis (TA) involved only pulmonary arteritis. Prednisone (PSL) 30 mg/day and beraprost improved her symptoms, inflammation, and imaging. Though TA with PH flared twice, dose escalation of PSL and addition of cyclosporine and mizoribine ameliorated it. Case 2: Twenty seven year old woman presented 5 month history of fever, back pain, and palpitation on exertion. PH was diagnosed by RHC (mPAP 31 mmHg). She was detected serum CRP elevation and enhanced stenosis of bilateral PA and dilation of ascending aorta by MRI, and diagnosed TA. PET-CT revealed FDG accumulation on bilateral PA, ascending aorta, and right myocardium. PSL (40 mg/day) and beraprost improved her symptoms, inflammation, and imaging. Conclusion: Though PH by TA is rare, we should consider TA when encounter PH cases, because it is sensitive for immunosuppressant therapy and expected to avoid irreversible change by early therapy.

#### W4-3

##### **Our experience with three cases of otitis media with ANCA-associated vasculitis**

Masami Mizuno, Taro Fujisawa, Takuo Hirota, Yukio Horikawa, Jun Takeda

Department of Immunology & Endocrinology, Gifu University Hospital, Gifu, Japan

Conflict of interest: None

[Case] A 78-year-old man developed otitis media around 2010. In May 2014, his hearing deteriorated and bilateral exudative otitis media was diagnosed. His hearing did not improve; thus, low-dose oral prednisolone (PSL) was started with a diagnosis of eosinophilic otitis media, but there was no improvement and fever and renal dysfunction developed. He was then referred and admitted to our department. Based on the MPO-ANCA positivity and histopathological findings of middle ear granulation tissue, he was diagnosed as having granulomatosis with polyangiitis complicated by ANCA-associated vasculitis (OMAAV). Steroid mini-pulse therapy was performed, followed by oral treatment with PSL 30 mg and ST combination. After the start of this therapy, his fever subsided and inflammatory reaction and renal function improved markedly. His hearing also somewhat improved. [Discussion] The Japan Otological Society has proposed the disease concept "OMAAV" as a possible cause for intractable otitis media in adults. OMAAV can be classified as granulomatous or executive otitis media type. Otitis media is often the initial symptom of this disease. OMAAV is difficult to diagnose and hearing deterioration often progresses. Here we report 3 cases of OMAAV, including this case, encountered in our hospital.

#### W4-4

##### **Twenty seven cases of otitis media with ANCA associated vasculitis**

Takeshi Nakatsue<sup>1</sup>, Chinatsu Takai<sup>1</sup>, Ayako Wakamatsu<sup>1</sup>, Yukiko Nozawa<sup>1</sup>, Hiroe Sato<sup>1</sup>, Yoko Wada<sup>1</sup>, Takeshi Kuroda<sup>2</sup>, Masaaki Nakano<sup>3</sup>, Ichiei Narita<sup>1</sup>

<sup>1</sup>Division of Clinical Nephrology and Rheumatology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan, <sup>2</sup>Health Administration Center, Niigata University, Niigata, Japan, <sup>3</sup>School of Health Sciences, Faculty of Medicine, Niigata University, Niigata, Japan

Conflict of interest: None

[Objectives] Otitis media is one of the upper respiratory lesions of granulomatosis with polyangiitis (GPA). We clarify clinical features of otitis media with ANCA associated vasculitis (OMAAV). [Methods] Twenty seven patients (thirteen males, fourteen females) with OMAAV who were admitted to Niigata University Medical and Dental Hospital from 1989 through 2014 were recruited. [Results] Fifteen patients were diagnosed as having GPA. Five were suspected having GPA. In seven patients, ANCA associated vasculitis (AAV) was suspected. Some biopsies were tried in 18 cases and histopathological findings of vasculitis were detected in 11 cases. The initial symptoms in 22 patients (81 %) were ears' one, such as congested feeling, impaired hearing, otalgia, or otorrhea. MPO- and PR3-ANCA were positive in 19 (70 %) and 6 cases (22 %), respectively. Hypertrophic pachymeningitis was observed in seven cases (26 %). Facial palsy was seen in three cases (11 %). Otitis media was involved in bilateral ears in 19 cases (70 %) and in unilateral in eight cases (30 %). The periods from the onset to the measuring ANCA were 0.6 to 21 months (6.5 +/- 5.9 months). [Conclusion] Since otitis media is one of the initial lesions of AAV, measuring ANCA should be considered in refractory otitis media.

#### W4-5

##### **Two Cases of ANCA-associated vasculitis complicated with central diabetes insipidus**

Keiji Ohashi, Michiko Morishita, Takayuki Katsuyama, Ken-ei Sada, Yosuke Asano, Yoshia Miyawaki, Eri Katsuyama, Haruki Watanabe, Noriko Tatebe, Koichi Sugiyama, Katsue Sunahori Watanabe, Hiroshi Wakabayashi, Tomoko Kawabata, Jun Wada, Hirofumi Makino

Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine Dentistry and Pharmaceutical Sciences, Okayama, Japan

Conflict of interest: None

Case 1: An 84-year-old woman with microscopic polyangiitis (MPA). During the course of the disease, brain MRI detected hypertrophic pachymeningitis (HP). Eight years after the onset, MPA relapsed and mPSL pulse therapy was initiated and coincidentally diagnosed as central diabetes insipidus (DI) based on polyuria, dry mouth, high urine osmolality and loss of high-intensity signals of the posterior pituitary. The treatment with desmopressin nasal spray (DDAVP) improved her symptoms and it was discontinued. Case 2: A 72-year-old woman with granulomatosis with polyangiitis (GPA). One year after the onset, GPA relapsed with headache and the diagnosis of central DI was made based on polyuria and the loss of high-intensity signals at the posterior pituitary. The pituitary biopsy demonstrated the presence of HP coexisted. The association of DI with ANCA-associated vasculitis (AAV) has been reported, while concomitant onset of both HP and DI is rare. Although most patients in previous reports required the permanent treatment with DDAVP, one of our cases was free of DDAVP administration. Pituitary involvement is rare but should not be overlooked especially in the AAV patients complicated with HP.

#### W4-6

##### **Five cases of MPO-ANCA-positive vasculitis with hypertrophic pachymeningitis**

Aya Imafuku, Naoki Sawa, Masahiro Kawada, Koki Mise, Rikako Hiramatsu, Keiichi Sumida, Eiko Hasegawa, Noriko Hayami, Tatsuya Suwabe, Junichi Hoshino, Yoshifumi Ubara, Kenmei Takaichi Toranomon Hospital

Conflict of interest: None

**[Introduction]** Hypertrophic pachymeningitis (HP) is a rare disease. We report the clinical characteristics of five cases of MPO-ANCA-positive vasculitis with HP. **[Result]** There were a man and 4 women with a mean age of 70.2 years. The clinical features at the presentation were headache in 4, and cranial nerve palsy in 3 cases. A gadolinium-enhanced brain MRI scan demonstrated pachymeningeal thickening in all cases. Examination of cerebrospinal fluid (CSF) revealed elevated pressure in 3, elevated cell count in 2, elevated protein in 2, and IgG index was elevated in all cases. The serum level of CRP was  $8.2\pm 4.6$  mg/dL, and the MPO-ANCA titer were elevated in 3 cases. Glomerulonephritis was evident in all cases, interstitial pneumonia was evident in 2, serous otitis media was evident in 4, and sigmoiditis was evident in 1 case. Though all cases were diagnosed with microscopic polyangiitis (MPA) at the onset of vasculitis, 4 cases were categorised into granulomatosis with polyangiitis (GPA) later. All cases improved well with corticosteroid therapy, 2 cases relapsed. **[Conclusion]** When patients with ANCA-associated vasculitis complain of headache or neurological abnormality, it is important to consider the possibility of HP and carry out a gadolinium-enhanced brain MRI.

### W5-1

#### **Latent tuberculosis infection diagnosed by the combination of interferon gamma release assay and chest X-ray in rheumatoid arthritis patients**

Akira Okamoto, Tetsuji Kawamura, Yasutaka Onishi, Rinko Katsuda, Kohei Miyake  
National Hospital Organization Himeji Medical Center

Conflict of interest: None

**[Objectives]** It is necessary to screen rheumatoid arthritis (RA) patients for latent tuberculosis infection (LTBI) before starting treatment. Recently, interferon gamma release assays (T-SPOT.TB) can be performed to detect LTBI. We studied the utility of T-SPOT.TB combined with chest X-ray, and the clinical features of LTBI in RA. **[Methods]** We performed T-SPOT.TB and chest X-ray in 184 RA patients (mean age,  $68.1\pm 11.4$  y.o.). **[Results]** On T-SPOT.TB, 39 patients (21.2%) were positive, 135 patients (73.4%) were negative, 4 patients (2.2%) were indeterminate, and 6 patients (3.3%) were borderline. Chest X-ray showed previous inactive tuberculosis in 14 patients (7.7%). Forty-seven patients (25.5%) had LTBI, i.e., a positive T-SPOT.TB or presence of abnormalities on chest X-ray. Among the 47 LTBI patients, 6 patients (12.8%) had both positive T-SPOT.TB and abnormalities on chest X-ray, 33 patients (70.2%) had only positive T-SPOT.TB, and 8 patients (17.0%) had only abnormalities on chest X-ray. All LTBI patients were 50 y.o. or above (mean age,  $72.4\pm 9.1$  y.o.). **[Conclusion]** Elderly RA patients require both T-SPOT.TB and chest X-ray for detection of LTBI.

### W5-2

#### **A prospective study of the standardized incidence ratio (SIR) of tuberculosis (TB) in patients with RA by *NinJa* cohort data for 11 years**

Yasuhiro Yoshinaga<sup>1</sup>, Tetsushi Aita<sup>1</sup>, Susumu Nishiyama<sup>1</sup>, Shoji Miyawaki<sup>1</sup>, Akira Okamoto<sup>2</sup>, Shigeto Tohma<sup>3</sup>  
<sup>1</sup>Rheumatic Disease Center, Kurashiki Medical Center, Kurashiki, Japan, <sup>2</sup>Department of Rheumatology, Himeji Medical Center, National Hospital Organization, Himeji, Japan, <sup>3</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, National Hospital Organization, Sagami, Japan

Conflict of interest: None

**[Objectives]** To evaluate the characteristics of the newly developed tuberculosis (TB) in the registered patients in *NinJa* cohort study for rheumatoid arthritis (RA). **[Methods]** We calculated the standardized incidence ratio (SIR) of TB from the clinical data on National Database of Rheumatic Disease by iR-net in Japan (*NinJa*) prospectively from 43 facilities for 11 years. **[Results]** Among 80,389 RA patients registered from 2003 to 2013, 60 patients developed TB and the SIR of TB was 3.33 (95%CI: 2.49-4.17). 7 patients (11.7%) were treated with biologic agents, and the SIR of TB in RA patients treated with biologic agents was 2.64 (0.33-4.95), and 32 patients (36.7%) were treated with MTX. The mean

age of them was 66.3 years old and the mean duration of RA before the onset of TB was 12.2 years. **[Conclusion]** Similarly our last year's report, the incidence of TB in RA patients was in the downward trend. By this study, in elderly, in patients with RA of long-term morbidity is the high risk of the newly developed TB.

### W5-3

#### **Epstein-Barr virus reactivation in patients with collagen tissue disease**

Yumi Iwasaku, Shusaku Fukaya, Shunji Yoshida  
Section of Rheumatology and Infectious Diseases, Department of Internal Medicine, Fujita Health University School of Medicine, Aichi, Japan

Conflict of interest: None

**[Objectives]** To clarify the definite status of Epstein-Barr virus (EBV) reactivation in connective tissue disease (CTD) patients. **[Methods]** About 188 patients with CTD receiving immunosuppressive therapy were enrolled in this study; of these, 158 patients showed symptoms of suspected viral infection and 30 patients were asymptomatic. Asymptomatic patients provided informed consent. EBV reactivation was determined on the basis of detection of EBV-DNA by real-time PCR. **[Results]** EBV-DNA detection rate was not significantly different for the symptomatic and asymptomatic groups (24.1% vs. 20.0%); however, it was relatively higher for patients with lymph node swelling compared to those without lymph node swelling (61.5% vs. 20.6%). If the cut-off value for EBV-DNA copy number is set to 1485 copies/ng-DNA, based on the results obtained by real-time PCR, it is possible to diagnose malignant lymphoma with a sensitivity of 72.7% and a specificity of 96.1%. **[Conclusion]** In CTD patients, EBV reactivation occurs at a high rate, irrespective of the presence or absence of symptoms. EBV reactivation occurs at a high rate in malignant lymphoma too; thus, EBV-DNA copy number is likely to be useful in the diagnosis of malignant lymphoma.

### W5-4

#### **Epstein Barr virus-positive mucocutaneous ulcer in stomach in a rheumatoid arthritis patient treated with methotrexate and abatacept**

Hiroki Araki, Toru Sakairi, Kazuhiko Uchiyama, Hiroko Hamatani, Noriyuki Sakurai, Hidekazu Ikeuchi, Yoriaki Kaneko, Akito Maeshima, Keiju Hiromura, Yoshihisa Nojima  
Medicine and Clinical Science, Gunma University Graduate School of Medicine

Conflict of interest: None

**[Case]** A 76-years-old male with rheumatoid arthritis was admitted to the hospital due to a huge gastric ulcer all around a pyloric zone. He had been treated with prednisolone and methotrexate (MTX) for 15 years, and abatacept (ABA) for 8 months. Biopsies from fundus of the ulcer showed inflammatory cell infiltration. After admission, a proton pump inhibitor was administered. ABA was stopped. Four months after the onset, the ulcer was not improved and biopsies revealed proliferation of lymphocytes including atypical cells. Immunostaining showed infiltration of EBER (+) cells and CD30 (+) large atypical cells, which were also observed in the specimens obtained at the onset. The diagnosis of Epstein-Barr virus (EBV)-positive mucocutaneous ulcer was made and MTX was discontinued. One month later, the ulcer was partially improved, and the EBER (+) cells and atypical cells were reduced. **[Discussion]** Reactivation of EBV during immunosuppression is associated with lymphoproliferative disorder (LPD). EBV-positive mucocutaneous ulcer, histologically characterized by polymorphous background infiltrate and presence of Reed-Sternberg cells, has been recently recognized as a new entity in EBV-LPD. EBV-LPD should be considered as a cause of gastric ulcer in patients under immunosuppression.

### W5-5

#### **Clinical characteristics of lung disease in rheumatoid arthritis patients with high levels of $\beta$ -D-glucan, and no evidence of *Pneumocystis***

Tomoya Harada, Masanori Hanaoka, Takahisa Gono, Eri Sato, Yasuhiro Katsumata, Eiichi Tanaka, Yasushi Kawaguchi, Hisashi Yamanaka  
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Objectives] Pneumocystis pneumonia (PCP) is one of life-threatening complications in patients with rheumatoid arthritis (RA). Actually, there are some patients who show ground-glass opacities (GGO), high levels of  $\beta$ -D-glucan ( $\beta$ -DG), and no detection of Pneumocystis by microscopic examination and PCR. [Methods] 30 patients who showed diffuse GGO and high levels of  $\beta$ -DG ( $>20$  pg/mL) were enrolled in this study. We defined patients in whom Pneumocystis was found by histochemical staining and/or PCR as a definite PCP subset ( $n=19$ ), and those in whom Pneumocystis was not found by the methods described above as a possible PCP subset ( $n=11$ ). We retrospectively compared clinical characteristics between the two subsets. [Results] Methotrexate was administered to all the patients. The median levels of  $\beta$ -DG was higher in the definite PCP subset than the possible PCP subset. In the possible PCP subset, age was younger, lower dose of prednisolone was treated with RA and serum levels of IgG was higher as compared to the definite PCP subset. [Conclusions] In patients who showed diffuse GGO and no evidence of Pneumocystis, risk factors for development of PCP is lacking despite of high levels of  $\beta$ -DG. The pathophysiology of lung disease revealed in these patients might be different from that of PCP.

## W5-6

### Study of Prognostic Factors Associated with Death from Pneumocystis Pneumonia Complicated by Connective Tissue Diseases

Ryo Yanai, Yusuke Miwa, Kuninobu Wakabayashi, Takahiro Tokunaga, Masayu Umemura, Sakiko Isojima, Hidekazu Furuya, Ryo Takahashi, Nobuyuki Yajima, Tsuyoshi Kasama  
Division of Rheumatology Department of Medicine, Showa University School of Medicine

Conflict of interest: None

[Objectives] To study prognostic factors associated with death from pneumocystis pneumonia (PCP) complicated by collagen diseases. [Methods] A retrospective study was conducted by dividing 38 patients who were diagnosed with PCP into a group of 31 survivors and a group of 7 non-survivors. For background factors, age, gender, smoking history, complications, underlying diseases, steroid dose were examined. For laboratory data, WBC, lymphocyte count, Hb, Cr, eGFR, albumin, LD, CRP, IgG, IgA, KL-6, SP-D,  $\beta$ -D glucan, PaO<sub>2</sub> / FiO<sub>2</sub> ratio, sputum PCP (by PCR) were tested. For methods of treatment, we studied TMP-SMX, the use of pentamidine, pulsed-steroid therapy, intratracheal intubation, admission to ICU, and a hospitalization period. [Results] In comparison to the cases of survivors, the cases of non-survivors had more men ( $p=0.021$ ), older age ( $p=0.029$ ), a higher serum Cr ( $0.88\pm 0.38$  mg/dl vs.  $1.16\pm 0.38$ ,  $p=0.045$ ), a lower alb ( $3.13\pm 0.50$  g/dl vs.  $2.71\pm 0.38$ ,  $p=0.031$ ), a higher CRP ( $7.8\pm 7.0$  mg/dl vs.  $18.9\pm 8.8$ ,  $p=0.014$ ), a lower IgA ( $274\pm 108$  mg/dl vs.  $174\pm 54$ ,  $p=0.013$ ), a higher SP-D ( $p=0.047$ ), a lower PaO<sub>2</sub> / FiO<sub>2</sub> ratio ( $268\pm 99$  mmHg vs.  $147\pm 98$ ,  $p=0.025$ ), and a higher rate of sputum PCP positive ( $p=0.035$ ). [Conclusion] In this study, we newly identified prognostic factors associated with death from PCP.

## W6-1

### The Usefulness of Cytomegalovirus Infection Monitoring based on The Guideline of Hematopoietic Cell Transplantation 2011 in Patients with Connective Tissue Disease

Takashi Nakanishi, Hideyuki Horikoshi, Rika Yonezawa, Satsuki Aochi, Reiko Takahashi, Fumihiko Kimura, Kenji Itoh  
Division of Hematology and Rheumatology, Department of Internal Medicine, National Defense Medical College

Conflict of interest: None

Objectives There is no official guideline for monitoring cytomegalovirus (CMV) infection in the patients with connective tissue diseases (CTD) under immunosuppressive treatment (IST). CMV infection monitoring according to the guideline of hematopoietic cell transplantation (HCT) was performed in CTD patients and its usefulness was evaluated. Methods Fifty-one CTD patients receiving  $\geq 20$  mg/day of prednisolone were monitored for CMV infection according to the guideline. Results

Thirty-seven events of the positive CMV pp65 antigen occurred in the 51 patients. According to the guideline, ganciclovir was administered in 23 of the 37 events (treatment group). The patients did not get treatment in the remaining 14 events (observation group). One patient in treatment group died of interstitial pneumonia. Persistent major organ involvement due to CMV did not occur in both groups. The risk factors for CMV infection were older age, steroid pulse therapy, and diabetes mellitus. The risk factors for CMV disease were cancer carrier status and CMV test positivity in the initial phase of steroid therapy. The most common symptom of CMV disease was thrombocytopenia. Conclusion This study demonstrates the usefulness of CMV infection monitoring according to the HCT guideline for CTD patients under IST.

## W6-2

### Cytomegalovirus infection in patients with rheumatic disease

Akiko Okamoto<sup>1</sup>, Mai Okubo<sup>1</sup>, Daisuke Tsukui<sup>1</sup>, Kurumi Asako<sup>1</sup>, Yoko Oguchi<sup>1</sup>, Zen-ichiro Honda<sup>1</sup>, Akiteru Takeuchi<sup>1</sup>, Toshihiro Nanki<sup>2</sup>, Hiroto Kikuchi<sup>1</sup>, Hajime Kono<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Teikyo University School of Medicine, <sup>2</sup>Teikyo Academic Research Center

Conflict of interest: None

[Objectives] To investigate the usefulness of the cytomegalovirus (CMV) antigenemia testing in patients with rheumatic diseases. [Methods] We reviewed 65 records for March to October 2014 and analyzed laboratory data including the CMV antigenemia testing and treatment in rheumatic disease patients. [Results] 25 patients were positive and 42 patients were negative for the CMV antigenemia testing. 15 patients received antiviral therapy (positive and treated group). Two had retinitis and three had gastrointestinal diseases. Corticosteroid dose was significantly higher for positive and treated group than negative group (mean 39mg/day vs 18.1mg/day). The lymphocyte count and the level of serum albumin was significantly lower for positive and treated group than negative group. Two patients were ganciclovir resistant and treated with foscarnet. [Conclusion] Screening of the CMV antigenemia testing may be beneficial for the patients treated with high dose corticosteroids or patients with decreased lymphocyte counts.

## W6-3

### Clinical usefulness of anti-hepatitis B virus (HBV) prophylaxis in hepatitis B surface (HBs) antigen -positive patients with rheumatoid arthritis (RA)

Kaoru Arii<sup>1</sup>, Munetoshi Nakashima<sup>2</sup>, Wataru Fukuda<sup>3</sup>, Tadamasu Hanyu<sup>4</sup>, Shinichi Mizuki<sup>5</sup>, Masaki Katayama<sup>6</sup>, Toshihisa Kanamoto<sup>7</sup>, Masayuki Miyata<sup>8</sup>, Yuichi Handa<sup>9</sup>, Yoshinobu Koyama<sup>10</sup>, Hiroyuki Hagiya<sup>11</sup>, Toshiyuki Kitaori<sup>12</sup>, Yoshinori Urushidani<sup>13</sup>, Takahito Yamazaki<sup>14</sup>, Atsushi Omoto<sup>15</sup>, Shigeo Inokuma<sup>16</sup>

<sup>1</sup>Department of Internal Medicine, Japanese Red Cross Kochi Hospital, Kochi, Japan, <sup>2</sup>Department of Rheumatology, Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan, <sup>3</sup>Center for Rheumatic Disease, Japanese Red Cross Society Kyoto Daiichi Hospital, Kyoto, Japan, <sup>4</sup>Department of Rheumatology, Nagaoka Red Cross Hospital, Niigata, Japan, <sup>5</sup>Department of Rheumatology, Matsuyama Red Cross Hospital, Ehime, Japan, <sup>6</sup>Department of Rheumatology, Osaka Red Cross Hospital, Osaka, Japan, <sup>7</sup>Department of Orthopedics, Nagano Red Cross Hospital, Nagano, Japan, <sup>8</sup>Department of Internal Medicine, Fukushima Red Cross Hospital, Fukushima, Japan, <sup>9</sup>Department of Rheumatology, Saitama Red Cross Hospital, Saitama, Japan, <sup>10</sup>Department of Rheumatology, Okayama Red Cross Hospital, Okayama, Japan, <sup>11</sup>Department of Rheumatology, Yokohama-City Bay Red Cross Hospital, Yokohama, Japan, <sup>12</sup>Department of Orthopedics, Fukui Red Cross Hospital, Fukui, Japan, <sup>13</sup>Department of Rheumatology, Matsue Red Cross Hospital, Shimane, Japan, <sup>14</sup>Department of Rehabilitation, Japanese Red Cross Society Kyoto Daini Hospital, Kyoto, Japan, <sup>15</sup>Center for Rheumatic Disease, Japanese Red Cross Society Kyoto Daiichi Hospital, Kyoto, Japan, <sup>16</sup>Department of Allergy and Rheumatic Diseases, Japanese Red Cross Medical Center, Tokyo, Japan

Conflict of interest: None

[Objectives] To identify the risk of immunosuppressive therapy relat-

ed hepatitis and evaluate the influences of anti-HBV prophylaxis on therapeutic target or prescription for RA in HBs antigen (HBsAg)-positive RA patients. [Methods] We registered HBsAg-positive, or -negative and hepatitis B core and/or HBs antibodies-positive RA patients treated with steroids, immunosuppressants or biological preparations in red cross hospitals in Japan, and established a database. In this study, 54 HBsAg-positive RA patients registered in the initial year were selected from the database, and the patient characteristics, agents for RA, and some RA disease activity scores were cross-sectionally investigated. [Results] The DAS28-ESR and -CRP levels in an HBV-DNA-positive group were significantly higher than in an HBV-DNA-negative group. There were no differences in agents for RA between the two groups. On the other hand, the DAS28-ESR, and -CRP levels in an anti-HBV prophylaxis group were significantly lower than in a non-prophylaxis group. Biological preparations, MTX, or TAC was administered to a significantly higher proportion of patients in the anti-HBV prophylaxis group. [Conclusion] This study showed that anti-HBV prophylaxis for HBsAg-positive RA patients facilitated positive RA treatment.

#### W6-4

##### **Vaccination guideline for pediatric rheumatic diseases: Recommendation of Pediatric Rheumatology Association of Japan**

Ichiro Kobayashi<sup>1</sup>, Masaaki Mori<sup>2</sup>

<sup>1</sup>Department of Pediatrics, Hokkaido University Graduate School of Medicine, <sup>2</sup>Department of Pediatrics, Yokohama City University Hospital

Conflict of interest: None

[Objectives] Pediatric Rheumatology Association of Japan has developed evidence-based guideline of vaccination in pediatric rheumatic diseases (PRDs). [Methods] Articles on vaccination in both adult and pediatric rheumatic diseases were searched in on-line databases or by hand-searching. Evidence levels and recommendation were graded according to Minds. [Results] Non-live vaccines are generally safe and effective in patients with PRDs on corticosteroid (GC), immunosuppressant (IS), and/or biologics, although efficacy may be attenuated under high dose of the drugs. However, efficacy and safety of live-attenuated vaccine for the patients on such medication has not been established. Thus, live-attenuated vaccines should be withheld and, if indicated, may be considered as a clinical trial under the approval by IRB. All patients with PRDs anticipating treatment with IS or biologics should be screened for infection of hepatitis B and C and tuberculosis before the commencement of medication. Varicella vaccine should be considered in sensitive patients ideally 3 weeks or longer before the commencement of IS, GC, or biologics. BCG should be withheld at least for 6 months after birth, if their mothers have received anti-TNF- $\alpha$  antibodies during the second or third trimester of pregnancy.

#### W6-5

##### **Frequency and clinical characteristics of fasciitis complicated with autoimmune diseases**

Kentarō Noda, Yosuke Oto, Kazuhiro Otani, Masayuki Yoshiga, Haruyasu Ito, Kenichiro Hirai, Kazuhiro Furuya, Yaro Ukichi, Ken Yoshida, Isamu Kingetsu, Daitaro Kurosaka

Division of Rheumatology, Department of Internal Medicine, The Jikei University School of Medicine

Conflict of interest: None

[Objectives] We determined the frequency and clinical characteristics of fasciitis in autoimmune diseases. [Methods] We retrospectively reviewed the medical records of patients diagnosed with dermatomyositis (DM), polymyositis (PM), systemic lupus erythematosus (SLE), and adult-onset Still's disease (AOSD), who presented with muscle weakness, myalgia, or increased levels of muscle enzymes between April 2007 and December 2013. We analyzed the frequency of fasciitis in autoimmune diseases by MRI and pathological findings of en bloc biopsy, as well as the association between muscular symptoms, muscle enzymes, and fasciitis. [Results] We identified 63 cases of autoimmune diseases. By MRI, fascial involvement was detected in 23 of 26 DM cases, 7 of 9 clinically amyopathic DM cases, 7 of 19 PM cases, 7 of 7 SLE cases, and 2 of 2 AOSD cases. Fascial involvement occurred at a high frequency in DM ( $p$

$< 0.01$ ) and a low frequency in PM ( $p < 0.01$ ). Histopathologically, fasciitis occurred at a high frequency in DM ( $p < 0.05$ ). Myalgia was associated with fasciitis ( $p < 0.05$ ), and there was no association between muscle weakness, muscular enzymes and fasciitis. [Conclusion] The fascia may be a target organ of autoimmune diseases and fascial inflammation may cause myalgia.

#### W6-6

##### **Now diagnostic method of renal amyloidosis in urine samples in patients with reactive amyloidosis associated with rheumatoid arthritis**

Takeshi Kuroda<sup>1</sup>, Ayako Wakamatsu<sup>1</sup>, Chinatsu Takai<sup>1</sup>, Hiroe Sato<sup>1</sup>, Takeshi Nakatsue<sup>1</sup>, Yoko Wada<sup>1</sup>, Masaaki Nakano<sup>2</sup>, Toshiyuki Yamada<sup>3</sup>, Ichiei Narita<sup>1</sup>

<sup>1</sup>Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, <sup>2</sup>Department of Medical Technology, School of Health Sciences, Faculty of Medicine, Niigata University, Niigata, Japan, <sup>3</sup>Department of Clinical Laboratory Medicine, Jichi Medical School, Tochigi, Japan

Conflict of interest: None

[Objectives] To examine amyloid protein in urine samples and investigate qualitative analysis of renal amyloidosis in patients with reactive amyloidosis associated with rheumatoid arthritis (RA). [Methods] The urine samples of RA patients with amyloidosis were centrifuged. The sediments were solubilized and blotted by anti-SAA antibody recognized common AA size (AA76). Urine sediments were stained with Congo-red. Immunohistochemical staining of urine sediments was performed using monoclonal antibodies against human SAA, podocarinin, megalin, aquaporin1 (AQP1) and aquaporin2 (AQP2). [Results] In urine sediments, Congo-red positive particles were detected and anti-SAA antibody stain also detected positive particle. These sediments were also detected SAA, podocarinin, megalin, AQP1 and AQP2. Double stains with anti-SAA antibody and antibodies detected with these renal components revealed that anti-SAA antibody positive particles, sediments stained with surface markers alone, and sediments coexistence with anti-SAA antibody positive particles and sediments stained with surface markers. [Conclusion] We have developed a non-invasive method for diagnosing renal amyloidosis associated with RA. This method represents as an alternative approach to evaluation of tissue biopsies.

#### W7-1

##### **Evaluation of the efficacy of biologic and targeted synthetic DMARDs toward rheumatoid arthritis (RA) patients by ultrasound (US): Kyushu multicenter rheumatoid arthritis ultrasound prospective observational cohort**

Ayako Nishino<sup>1</sup>, Shin-ya Kawashiri<sup>1,2</sup>, Atsushi Kawakami<sup>1</sup>, Tamami Yoshitama<sup>3</sup>, Nobutaka Eiraku<sup>3</sup>, Naoki Matsuoka<sup>3</sup>, Akitomo Okada<sup>3</sup>, Hiroaki Hamada<sup>3</sup>, Toshihiko Hidaka<sup>3</sup>, Keita Fujikawa<sup>3</sup>, Tomomi Tsuru<sup>3</sup>, Shuji Nagano<sup>3</sup>, Yukitaka Ueki<sup>3</sup>, Yojiro Arinobu<sup>3</sup>, Yoshiya Tanaka<sup>3</sup>, Hiroaki Ida<sup>3</sup>, Takaaki Fukuda<sup>3</sup>, Katsuya Kanesaki<sup>3</sup>, Hideo Ohtsubo<sup>3</sup>, Tomomaro Izumihara<sup>3</sup>, Kiyoshi Migita<sup>3</sup>

<sup>1</sup>Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, <sup>2</sup>Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, <sup>3</sup>Kyushu Multicenter Rheumatoid Arthritis Ultrasound Prospective Observational Cohort Study Group

Conflict of interest: None

Objectives; Kyushu multicenter rheumatoid arthritis ultrasound prospective observational cohort has been initiated at June 2013. Based on this study, we have evaluated the efficacy of biologic and targeted synthetic DMARDs (b/ts DMARDs) toward RA patients by US. Methods; Disease activity were evaluated by US and clinical composite measures such as DAS28, SDAI and CDAI every 3 months after induction of b/ts DMARDs. US assessment was done by 22 sites of bilateral wrist and finger joints. Each joint was scored for gray scale and power Doppler on scale from 0 to 3. Plain radiograph of both hands and feet were evaluated every 6 months. Results; A total of 109 RA patient were included by October, 2014, and we evaluated the 42 patients during 6 months (mean of age: 66 years-old, that of disease durations: 64.5 months) out of 109

patients in the present study. Clinical and US disease activity have improved significantly during 6 months. In early phase, TNF inhibitors exhibited better outcome in both clinical and US parameters as compared with TCZ or ABT. Discussion; It may be suggested that previous use of b/ts DMARDs or concomitant use of MTX influence early therapeutic responsiveness. We will discuss the detailed data with serum/plasma biomarkers after collecting the larger samples.

### W7-2

#### To assess usefulness of Power Doppler ultrasonography for rheumatoid arthritis patients treated with tocilizumab sc. (GATSU study)

Yumiko Sugiyama<sup>1</sup>, Maasa Hama<sup>1</sup>, Kiyomitsu Miyachi<sup>2</sup>, Nobuyuki Gonda<sup>3</sup>, Kenichi Miyagi<sup>4</sup>, Yukihiro Toyota<sup>1</sup>, Naomi Tsuchida<sup>1</sup>, Yosuke Kunishita<sup>1</sup>, Daiga Kishimoto<sup>1</sup>, Reikou Kamiyama<sup>1</sup>, Kaoru Minegishi<sup>1</sup>, Ryusuke Yoshimi<sup>1</sup>, Yohei Kirino<sup>1</sup>, Atsuhisa Ueda<sup>1</sup>, Yoshiaki Ishigatsubo<sup>1</sup>  
<sup>1</sup>Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, <sup>2</sup>Keigu Clinic, <sup>3</sup>Tomioka Naika Clinic, <sup>4</sup>Miyagi Naika Clinic

Conflict of interest: None

[Objectives] Though US is a potent tool for evaluating activity of synovitis in rheumatoid arthritis, it remains unclear whether US findings are related to clinical score, radiologic progression, and serum markers under subcutaneous tocilizumab (TCZ sc) therapy. [Methods] We prospectively analyzed clinical, US, and hand X-ray findings as well as serum VEGF level among patients who were initiated TCZ sc. Power Doppler (PD) signal was graded from 0 to 3 in 24 joints, and total PD score was calculated as the sum of scores of individual joint. US remission was defined as no PD signal in all joints. [Results] Fifteen patients were enrolled. Baseline activities were DAS28-ESR 5.6±1.4, SDAI 32±19, and CDAI 28±14, and total PD score was 8 (2-33). After 6 months, 86% achieved more than moderate response and 40% did Boolean remission, whereas none experienced radiologic progression. Total PD score reduced to 40%(27-100%). One patient achieved US remission. The level of VEGF decreased less than half of baseline after treatment in all patients except one whose VAS worsened accompanied by re-increase in MMP-3. [Conclusion] PD signal remained in most patients after 6-months successful treatment with TCZ sc. We need longer observation to clear the relationship between PD signal and joint destruction.

### W7-3

#### A Study of joint ultrasonography PD evaluation in hand joints

Masao Hiraga

Kirishima City Medical Association Medical Center

Conflict of interest: None

[Objection] We assessed the utility of Power Doppler ultrasonography of the wrist joint except the synovial membrane for early RA. [Methods] This study enrolled 13 patient with mild wrist pain (group A) and 49 healthy volunteer without wrist pain (group B). Two longitudinal image of the wrist, Navicular bone and Lunate bone (N line and L line) were depicted, and focused on the space between the extensor tendon and bone surface except synovial membrane with Power Doppler ultrasonography. All cases were examined using Linear probe of Ascendus, Noblus. According to the Power Doppler signal we divided the grade into 4 point; 0 point: no Power Doppler Signal (PDS); 1 point: 0.25mm≤PDS; 2points: 0.25<PDS≤0.5mm; 3points: PDS>0.5mm. N line and L line was divided into 3 portion and scored bilaterally. [Results] The average points from proximal to distal of Group B were in L-line rt. side 0.02, 0.22, 0.84, lt. side 0.02, 0.29, 0.78,N-line; rt. side 0.14, 0.41, 0.61. lt. side 0.16, 0.41, 0.51. And in Group A L-line rt. side 0.3, 1.1, 1.5, lt. side 0.4, 1.4, 1.7 N-line rt side; 1.0, 1.6, 2.0 lt. side 0.7, 1.7, 1.8. [Conclusion] PDS over 0.5mm was not detected in healthy volunteer. We showed the possibility that PDS on the bone of wrist joint can detect the early stage change of wrist joint.

### W7-4

#### Rheumatoid arthritis patients with positive power Doppler signals after the achievement of clinical remission should be treated more intensively? - SCRUM study -

Tadashi Okano<sup>1</sup>, Tatsuya Koike<sup>2,3</sup>, Kentaro Inui<sup>1</sup>, Masahiro Tada<sup>1</sup>, Yuko Sugioka<sup>2</sup>, Kenji Mamoto<sup>1</sup>, Hiroaki Nakamura<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan, <sup>2</sup>Center for Senile Degenerative Disorders (CSDD), Osaka City University Medical School, Osaka, Japan, <sup>3</sup>Search Institute for Bone and Arthritis Disease (SINBAD), Wakayama, Japan

Conflict of interest: None

[Objectives] The aim of this study was to assess subclinical synovitis through ultrasonography (US) and to evaluate the effects of intensive treatment on preventing the joint damage in patients with rheumatoid arthritis in clinical remission. [Methods] US examination was performed for 134 patients with RA in clinical remission defined as DAS28-CRP<2.6. According to the result of US assessment, the patients with active synovitis were randomly assigned in the group to be treated by increasing the dose of MTX (MTX increasing group) or the group to be continued their current treatment (MTX stable group) until week 52. Radiological joint damage was assessed according to the modified total Sharp score (TSS). [Results] In 101 (75.4%) patients with active synovitis at baseline, 51 patients were assigned to MTX increasing group and 50 patients were assigned to MTX stable group. The progression of TSS was significantly suppressed in MTX increasing group compared to MTX stable group at both week 24 (0.27 and 1.02, p=0.007, respectively) and week 52 (1.03 and 2.02, p=0.038, respectively). [Conclusion] US assessment is important even in patients with RA achieving remission, and the prevention of the joint damage progression should be considered in patients with subclinical active synovitis.

### W7-5

#### Radiographic changes in patient groups who achieved remission by introduction of biological agents (6 types)—Possibility of damaged joint repair—

Shunichi Imai<sup>1</sup>, Ken Hasegawa<sup>2</sup>

<sup>1</sup>Rheumatoid Arthritis Center, Minami Medical Health Cooperation, <sup>2</sup>Department of Orthopaedic Surgery, Meinan Hospital

Conflict of interest: Yes

[Objectives] To investigate radiographic changes with biological therapy and the possibility of damaged joint repair. [Methods] Patients who achieved clinical remission with biological therapy and received continuous treatment for more than 2 years were included. Radiographic evaluation was performed immediately before and 2 years after biological therapy using Larsen Grading Scale (improved, unchanged and worse) in 1417 joints of 87 patients treated with infliximab, etanercept, tocilizumab, adalimumab, abatacept or golimumab. [Results] Although the proportions of unchanged joints were nearly 80% for all agents, differences in the proportions of improved and worsened joints were confirmed between agents. Furthermore, in the case of the radiographic changes in grade III or higher severely damaged joints, differences in the proportions of improved and worsened joints were confirmed. [Conclusion] Approximately 80% of joint damage can be prevented if clinical remission is achieved with biological therapy. However, both improved and worsened joints were confirmed. Furthermore, even if the level of joint damage is severe, once clinical remission is achieved with biological therapy, improved joints are confirmed, suggesting the possibility of radiographic remission.

### W7-6

#### An investigation of CT findings of the sacroiliac joint

Maki Asada, Ryo Oda, Daisaku Tokunaga, Daigo Taniguchi, Shogo Toyama, Satoru Nakamura, Hiroyoshi Fujiwara, Toshikazu Kubo  
Department of Orthopaedics, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: None

[Objectives] Radiological findings of sacroiliitis are a prerequisite in diagnosing axial spondyloarthritis, but imaging studies of the sacroiliac joint (SIJ) are scarce. Our objective was to investigate the features of SIJ degeneration using CT images of hip osteoarthritis (OA) patients. [Methods] One-mm slice CT images of 26 hip OA patients (52 joints) including the SIJs taken preceding total hip arthroplasty were used. The Kellgren-Lawrence method was used to radiographically stage hip OA. [Results] Vacuum phenomena of the SIJ were seen in 45 joints on CT. On plain radiograph, 41 SIJs showed subchondral sclerosis, 5 of which were seen unilaterally. The hip OA stages were 0 in 7, 1 in 10, 2 in 3, 3 in 10, 4 in 22 joints respectively, and laterality of hip OA indicated by a difference of 2 stages or more were seen in 19 cases. Out of the 5 cases showing unilateral SIJ degeneration, 4 were seen contralateral to the more affected hip. [Conclusion] In our study, the incidence of SIJ degeneration, especially vacuum phenomena, was high at 87%, compared to previous reports in the normal population (30%). The unilateral SIJ degeneration tended to occur on the contralateral side to the more advanced stage of hip OA, suggesting a relationship between the pathology of these joints.

### W8-1

#### **Sonographic scoring of the shoulder synovitis and its surrogate maker are useful for discriminating polymyalgia rheumatica from elderly-onset rheumatoid arthritis**

Takeshi Suzuki, Akiko Okamoto

Division of Rheumatology, Department of Internal Medicine, Mitsui Memorial Hospital, Tokyo, Japan

Conflict of interest: None

[Objectives] To evaluate the discriminating ability of US scoring of shoulder synovitis and its surrogate maker to distinguish between polymyalgia rheumatic (PMR) and elderly-onset rheumatoid arthritis mimicking PMR (pm-EORA). [Methods] In consecutive 15 PMR and 15 pm-EORA patients, the severity of tenosynovitis of the long-head of the biceps, bursitis of shoulder including subdeltoid, subacromial and subcoracoid bursitis, and synovitis of glenohumeral joint were subjectively scored for GS and PD on a four-point scale: 0-3. Sum of the all scores of both shoulders was defined as "patient-synovitis score (PSS)", and the correlation between PSS and serum markers was assessed. [Results] PSS in PMR tended to be lower than in pm-EORA. PSS were positively correlated with serum MMP3. Both PSS and MMP3 were positively correlated with serum CRP in pm-EORA but not in PMR. Threshold for discriminating PMR from pm-EORA could be set for the ratio PSS/CRP or MMP3/CRP. By adding 1 point to the scores from 2012 PMR criteria without US in cases where the ratio was lower than the threshold, the optimal cut point became 5. Both ratio improved the specificity of the 2012 criteria. [Conclusion] US scoring of the shoulder synovitis and its surrogate maker are useful for discriminating PMR from EORA.

### W8-2

#### **Diagnostic accuracy of Rotator cuff tear in Musculoskeletal Ultrasound**

Akiko Sahara<sup>1</sup>, Kenta Misaki<sup>2</sup>, Rintaro Saito<sup>2</sup>, Yuri Nakamura<sup>2</sup>, Yoshie Gon<sup>2</sup>, Takumi Nagamoto<sup>2</sup>, Hisayo Horiuchi<sup>2</sup>, Hirotaaka Yamada<sup>2</sup>, Toshihiko Yokota<sup>2</sup>

<sup>1</sup>Kurashiki Central Hospital Laboratory Medicine, <sup>2</sup>Department of Endocrinology and Rheumatology, Kurashiki Central Hospital, Okayama, Japan

Conflict of interest: None

[Objectives] To evaluate that the diagnostic accuracy of rotator cuff tear by MSKUS was equivalent to MRI. [Methods] From Jan. 2012 to Oct. 2014, The 30 cases (31 examinations of shoulder joint by MSKUS) were enrolled. All cases performed MSKUS prior to MRI. The patient characteristics were as follows: female: 16, male: 14, age: mean 67.9 y.o. The basal diseases were RA: 17, PMR: 3, UA: 7, PsA: 1, SJS: 1 and SSC: 1. The definition of full-thickness tear (FTT) was tendon deficit and those of partial-thickness tear (PTT) were disappearing of tendon outer edge, thinning and appearance of intra-tendon low echoic area. The diagnostic accuracy between MSKUS and MRI was validated. [Results] Abnormal findings at rotator cuff in both MSKUS and MRI were detected in 17 cas-

es (FTT: 11, PTT: 6). Sensitivity, specificity and positive predictive value of MSKUS for FTT were 81.8%, 94.7% and 90.0%, respectively, and those for PTT were 100%, 40.0% and 28.5%, respectively. The diagnostic yield of remarkable FTT was 100%. [Conclusion] MSKUS is a useful and convenient examination for the diagnosis of rotator cuff with great accuracy, especially for the FTT. However, PTT were difficult to identify by means of MSKUS only.

### W8-3

#### **Ultrasonography evaluation of ankle is essential for rheumatoid arthritis patients in daily clinical practice**

Yukihiro Toyota<sup>1</sup>, Kaoru Minegishi<sup>1</sup>, Maasa Hama<sup>1</sup>, Ryusuke Yoshimi<sup>1</sup>, Yumiko Sugiyama<sup>1</sup>, Naomi Tsuchida<sup>1</sup>, Yosuke Kunishita<sup>1</sup>, Daiga Kishimoto<sup>1</sup>, Reikou Kamiyama<sup>1</sup>, Yohei Kirino<sup>1</sup>, Mitsuhiro Takeno<sup>2</sup>, Atsuhisa Ueda<sup>1</sup>, Yoshiaki Ishigatsubo<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan, <sup>2</sup>Clinical Laboratory Department, Yokohama City University Hospital, Yokohama, Japan

Conflict of interest: None

[Objectives] To examine the prevalence of tibiotalar arthritis and ankle tendon involvement in patients with rheumatoid arthritis (RA). [Methods] Fifty-six RA patients were included in this study [women 82%, age (mean±SD) 62±15]. Routine 8 joints (bilateral 2,3MCP, wrist, knee) and bilateral ankles (tibiotalar joint, anterior extensor tendons, posterior tibial tendon, peroneus longus/brevis tendon) were examined by gray scale (GS) and power Doppler (PD) ultrasonography (US). Synovitis and tenosynovitis was scored semiquantitatively (0-3). Visual analog scale (VAS) for patient assessed pain of ankle was also evaluated. [Results] A total of 112 ankle joints, positive GS/PD findings (GS≥2/PD≥1) were found in 24/25 joints (tibiotalar joint 12/10, anterior extensor tendons 4/2, posterior tibial tendon 7/9, peroneus longus/brevis tendon 7/9). Two patients showed positive PD findings in the tibiotalar joint, however these patients didn't have synovitis in routine 8 joints and their DAS28-ESR was clinical remission. Ankle VAS was significantly higher in patients having positive ankle US than in negative patients ( $P=0.006$ ). [Conclusion] True prevalence of ankle involvement is difficult to assess due to lack of standardized US technique. However, such involvement is a common in RA.

### W8-4

#### **A study of the imaging evaluation method for patients of rheumatoid arthritis with an x-ray Talbot-Lau interferometry**

Hiroyuki Yoshioka<sup>1</sup>, Hiromi Oda<sup>1</sup>, Yoon Taek Kim<sup>1</sup>, Toshihide Mimura<sup>2</sup>, Takashi Maruyama<sup>2</sup>, Junji Tanaka<sup>3</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Saitama Medical University, Faculty of Medicine, Saitama, Japan, <sup>2</sup>Department of Rheumatology and Applied Immunology, Saitama Medical University, Faculty of Medicine, Saitama, Japan, <sup>3</sup>Department of Radiology, Saitama Medical University, Faculty of Medicine, Saitama, Japan

Conflict of interest: None

[Objectives] An x-ray Talbot-Lau interferometry has high sensitivity to soft tissues. We evaluated the possibility of applying it to RA patients. [Methods] The imaging of two MP joints were carried out with 55 healthy volunteers (Averaged age 42.5, Male/Female: 15/40) and 42 RA patients (Averaged age 63.2, Male/Female 8/34, Steinbrocker classification Stage I/II/III/IV: 19/12/6/5). We evaluated the imaged MP joints by Larsen grading scale with conventional x-ray images and measured the thickness of the cartilage on metacarpals with images by x-ray Talbot-Lau interferometry. Additional images of some patients were obtained several months after the evaluation. [Results] The average thickness of the cartilage was 632µm with healthy volunteers and 553µm with RA patients, in which 594µm with Stage I and 543µm with Stage II by Steinbrocker classification, and 572µm with Grade 0 and 557µm with Grade I by Larsen grading scale. The thickness of the cartilage decreased according to the progress of RA. The difference of it between the healthy volunteer and the patients were significant, even though the patients were in early stage of RA. The image showed the progress of RA in the same pa-

tient. [Conclusion] An x-ray Talbot-Lau interferometry has a possibility to diagnose RA patients by imaging cartilage.

## W8-5

### Use of ultrasound and tomosynthesis can improve the diagnostic performance of early rheumatoid arthritis

Hideki Kasahara, Tomoko Tomita, Miyuki Bohgaki, Takao Koike  
Department of Rheumatology, NTT Sapporo Medical Center, Sapporo, Japan

Conflict of interest: None

[Objectives] To determine the respective diagnostic efficiency for early rheumatoid arthritis (RA) with radiography (X-P), tomosynthesis (Tomo), ultrasonography (US), and combinations of these imaging modalities. [Methods] One hundred patients with musculoskeletal symptoms who visited to our hospital from January 2012 to July 2014 were enrolled. Patients underwent clinical, laboratory, radiographic tests and US at baseline. The patient with RA was defined as who was prescribed DMARDs. RA was classified according to the classification criteria (EULAR 2010) using radiograph (1) X-P), tomosynthesis (2) Tomo), and/or Power Doppler  $\geq$  grade 2 in US and a score of  $> 5/10$  in the criteria (3) X-P+US, 4) Tomo+US). [Results] Sensitivity and specificity, positive predictive value, negative predictive value, likelihood ratio, likelihood ratio negative of the classification criteria were 1) (83.9%, 68.2%, 88.1%, 60%, 2.636, 0.237) vs 2) (95.2%, 68.2%, 89.4%, 83.3%, 2.991, 0.071) vs 3) (95.2%, 68.2%, 89.4%, 83.3%, 2.991, 0.071) vs 4) (98.4%, 68.2%, 89.7%, 93.8%, 3.092, 0.024), respectively. [Conclusion] Use of US and Tomo can improve the diagnostic performance of the classification criteria (EULAR 2010) because of earlier detection of bone erosions and synovitis.

## W8-6

### Comparative Study of Coincidence and Value of Ultrasonography and MRI in Patients with Undifferentiated Arthritis

Yasushi Kondo, Yuko Kaneko, Chihiro Takahashi, Yumiko Inoue, Kunihiro Yamaoka, Tsutomu Takeuchi  
Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Conflict of interest: Yes

[Objective] We examined the coincidences and the impact for the diagnosis to clarify the usability of ultrasonography (US) and MRI for patients with undifferentiated arthritis (UA). [Methods] We enrolled 30 UA patients who did not fulfilled EULAR/ACR RA classification criteria. All patients were performed US and enhanced MRI. US of the bilateral wrists, fingers and symptomatic joints were assessed. Positive of US defined as gray scale more than grade1. We calculated  $\kappa$  coefficient among physical examination, US and MRI for hand joints. We also examined how the results of imaging affect the development of recent RA criteria. [Result] Median age and symptomatic period were 61.2 years old and 3 months. Positivity of Anti-CCP and RF were 16% and 40%. Mean CRP level was 0.8 mg/dl. Swollen, tender joints have little match with MRI ( $\kappa=0.15$  and  $0.17$ ). High concordance of US and MRI was found in hand joints and tolerable in PIP ( $\kappa=0.82, 0.55$ ). After imaging 12 UA patients were met the RA criteria and 9 were after US. 3 patients who have mainly PIP arthritis could fulfill the criteria only after MRI. [Conclusion] Coincidence of US and MRI were quite better than physical examination in UA patients and using both imaging tests as the situation demands may improve the diagnostic sensitivity.

## W9-1

### Clinical and genetic features of familial Mediterranean fever in Japan

Dai Kishida, Akinori Nakamura, Masahide Yazaki, Ayako Suzuki, Kenichi Ueno, Yasuhiro Shimojima, Wataru Ishii, Masayuki Matsuda, Shuichi Ikeda  
Department of Neurology and Rheumatology, Shinshu University School of Medicine, Matsumoto, Japan

Conflict of interest: None

[Objectives] To elucidate the clinical characteristics of Japanese FMF patients and to examine the difference between Japanese and Mediterranean patients about clinical and genetic features. [Methods] We analyzed the *MEFV* genotypes and clinical manifestations in 116 patients clinically diagnosed as having FMF and with at least one mutation. [Results] The male/female ratio was 1:1.3. The mean age at onset of symptoms was 23.7 years, the mean frequency of attacks was 11.7 per year, and the mean duration of attacks was 4.7 days. The main clinical symptoms of the patients were as follows: high-grade fever was observed in 83.6% of the patients, peritonitis in 62.1%, pleuritis in 45.7%, and arthritis in 41.4%. Colchicine treatment was received 60.3% and most of them showed good response. The most frequent mutation in Japanese patients was E148Q (40.2%), followed by M694I (21.0%), L110P (18.8%). In contrast, common mutations seen in Mediterranean patients, such as M694V, V726A, and M680I, were not detected in this population. There was the correlation between specific genotype and phenotype. [Conclusion] Clinical and genetic features of Japanese FMF patients vary widely from Mediterranean patients. Both clinical and genetic analysis are needed for diagnosis in case of Japanese FMF.

## W9-2

### Clinical examination about patients with familial Mediterranean fever in our hospital

Hiroaki Ida<sup>1</sup>, Yukiko Kunitake<sup>1</sup>, Naomi Yoshida<sup>1</sup>, Daisuke Wakasugi<sup>1</sup>, Morihiro Tajiri<sup>1</sup>, Masaki Okamoto<sup>1</sup>, Masaki Tominaga<sup>1</sup>, Shinjiro Kaieda<sup>1</sup>, Kiyoshi Migita<sup>2</sup>, Takaaki Fukuda<sup>3</sup>

<sup>1</sup>Division of Respiriology, Neurology, and Rheumatology, Department of Medicine, Kurume University School of Medicine, Fukuoka, Japan, <sup>2</sup>National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan, <sup>3</sup>Kurume University Medical Center, Fukuoka, Japan

Conflict of interest: None

[Objectives] Familial Mediterranean fever (FMF) is the most popular autoinflammatory syndrome in Japan and is known to be important for the differential diagnosis of unknown fever. [Methods] We studied the clinical examination about 10 patients with FMF in our hospital. [Results] We diagnosed as a revised Tel-Hashomer criteria including periodic fever (10/10), chest pain (4/10), and abdominal pain (5/10), etc, and detected *MEFV* mutations, such as M694I in 2 patients and P369S/R408Q in 3 patients out of 10 genomic analyses. Colchicine treatment was effective in 9 patients out of 10. [Conclusion] FMF is an important disease for the differential diagnosis of periodic and unknown fever.

## W9-3

### Long-term experience of the canakinumab medical treatment to the familial cold-urticaria syndrome (FCAS) in three generations

Kaori Hisa<sup>1</sup>, Shigeru Nomura<sup>1</sup>, Tomoyuki Imagawa<sup>1</sup>, Ryuta Nishikomori<sup>2</sup>  
<sup>1</sup>Kanagawa Children's Medical Center, Kanagawa, Japan, <sup>2</sup>Department of Pediatrics, Graduate School of Medicine and Faculty of Medicine Kyoto University, Kyoto, Japan

Conflict of interest: None

[objectives] Adaptation of canakinumab medication of familial cold urticarial syndrome (FCAS) and a medication method were examined. [Method] The therapy of canakinumab, time of introduction, a given dose, and intervals were examined, which diagnosed it as FCAS (mutation: NLRP3 A439V hetero) [Result] The case 1 is a 5 y.o boy. Fever, a rash, headache, an arthritic pain repeated from infant. At 3 y.o came diagnosis of FCAS, and it accepted the improvement of the condition after canakinumab (2mg/kg/day). After the 7th week of the medication start, headache is accepted, it increases to 8mg/kg/day, and the symptom improvement. The case 2 (mother), Fever, erythema, arthritic pain are repeated after cold stimulation from child, and it is optic-nerve-inflammation. canakinumab (3mg/kg/8week) started, and symptom improvement. The case 3 (grandmother), arthritic pain, slight fever, stomachache, rash are repeated from child. Canakinumab (3mg/kg/8week) started, 59 y.o, and it is a symptom improvement. To maintain remission, the same quantity as other types of disease and an interval were required for the given



dose of canakinumab, and the interval. [Conclusion] Also in FCAS, canakinumab is effective, and was able to obtain the improvement of everyday life.

#### W9-4

##### Report of the gene analysis of the periodic fever patient in our Hospital

Miharu Izumikawa<sup>1</sup>, Kentaro Susaki<sup>1</sup>, Tomohiro Kameda<sup>1</sup>, Yohei Takeuchi<sup>1</sup>, Shusaku Nakashima<sup>1</sup>, Hiromi Shimada<sup>1</sup>, Hiroki Ozaki<sup>1</sup>, Risa Wakiya<sup>1</sup>, Hiroaki Dobashi<sup>1</sup>, Ryuta Nishikomori<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Division of Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University, Kagawa, Japan, <sup>2</sup>Department of Pediatrics, Kyoto University Graduate School of Medicine, Kyoto, Japan

Conflict of interest: None

[Objectives] The recognition is increasing since a disease concept called the autoinflammatory syndrome was proposed in 1999, but the case that does not lead to a diagnosis is thought to be present, and it is necessary to push forward the diagnosis that this disorder included a genetic analysis in mind for the unidentified periodic inflammatory disorder. We report on the results of the genetic analysis of eight patients presenting with undiagnosed periodic fever in this hospital. [Methods] About eight periodic fever disease that did not lead to the diagnosis that gave medical care in this hospital for three years from 2012 through 2014, we analyzed the representative gene (MEFV, TNFRSF1A, NLRP3) of the autoinflammatory syndrome. [Results] One patient definitively diagnosed cryopyrin related periodic fever syndrome (CAPS) in acknowledgment of a mutation in the gene of NLRP3 (D303A). MEFV (E148Q/L110P) compound heteromutation was detected in one patient, and one showed MEFV (E148Q/ P369S/ R408Q) compound heteromutation and diagnosed these two cases with familial Mediterranean fever (FMF). [Conclusion] By the genetic analysis of the 8 case that presented periodic fever disease, we diagnosed CAPS, two with one clinically with FMF.

#### W9-5

##### Clinical characteristics of four patients who present with repeated fever and systemic pain such as spondyloarthritis or fibromyalgia

Hitoshi Kobayashi<sup>1</sup>, Okinori Murata<sup>1</sup>, Kouko Kowata<sup>1</sup>, Nobuhito Sasaki<sup>1</sup>, Kohei Yamauchi<sup>1</sup>, Kiyoshi Migita<sup>2</sup>

<sup>1</sup>Division of Pulmonary Medicine, Allergy and Rheumatology, Department of Internal Medicine, School of Medicine, Iwate Medical University, <sup>2</sup>National Hospital Organization Nagasaki Medical Center

Conflict of interest: None

[Purpose] Mediterranean fever is one of the autoinflammatory disease to repeat periodic fever, and assumed to be related MEFV gene abnormality. Recently, it was reported that Fibromyalgia and Behcet's disease are associated with MEFV gene abnormality. This time, we describe about clinical characteristics of four cases with the periodic fever and with inflammatory back pain and sacroiliac joint pain like FM or SpA. Case 1, 37 years old woman. She had repeated red spots and arthralgia since 14 years old, and was diagnostic of SLE at 28 years old. Case 2; 54 years old woman. She had repeated pyelonephritis since 33 years old. Case 3; 39 years old woman. she noticed chronic urticarial at 33 years old. She repeated diarrhea, a slight fever, resting back pain, lumbago. Case 4; 36 years old woman. She repeated stomachache, fever for stomatitis for two years, and then complained of systemic pain. All cases meet 1990' FM classification of ACR and showed dactylitis, polyarthralgia, and resting backpain. Case1, 2, 3 present with MEFV gene abnormality, E148Q, R202Q, and G304R respectively. Treatment with prednisolone is effective in all cases, although colchicine was not. [Conclusion] It was suggested that some patients with episodic fever may be associated with the pathogenesis of FM or SpA.

#### W9-6

##### [Dysregulated mature IL-1 $\beta$ production in Familial Mediterranean fever

Kiyoshi Migita<sup>1</sup>, Fumiaki Nonaka<sup>2</sup>, Toshimasa Shimizu<sup>2</sup>, Nozomi

Iwanaga<sup>1</sup>, Yasumori Izumi<sup>1</sup>, Yoshika Shigemitsu<sup>1</sup>, Keita Fujikawa<sup>3</sup>, Hiroshi Furukawa<sup>4</sup>, Atsushi Kawakami<sup>5</sup>, Katsumi Eguchi<sup>1</sup>

<sup>1</sup>Nagasaki Medical Center, National Hospital Organization, <sup>2</sup>Sasebo City General Hospital, <sup>3</sup>JCHO Isahaya General Hospital, <sup>4</sup>NHO Sagamiara Hospita, <sup>5</sup>Department of Rheumatology, Nagasaki University Hospital

Conflict of interest: None

[Objectives] The aim of this study was to analyze the role of circulating cleaved IL-1 $\beta$  in patients with Familial Mediterranean fever (FMF). [Methods] We enrolled 20 patients with FMF (5 males and 15 females), 22 patients with RA (4 males and 18 females) and 22 healthy controls (6 males and 16 females). We determined whether IL-1b was present as the cleaved form (p17) in the sera of FMF patients by immunoblotting using anti-cleaved IL-1 $\beta$  antibody. [Results] Immunoblot analysis demonstrated that the cleaved form of IL-1b (p17) was present in the sera from FMF patients during febrile attack periods, but not in patients with RA or healthy controls. The amounts of cleaved IL-1 $\beta$ (p17) were significantly higher in patients with FMF compared to those in patients with RA. [Conclusion] The cleaved form of IL-1 $\beta$  is a valuable biomarker for patients with FMF.

#### W10-1

##### Investigation of factors influencing physical function mid-term status after total joint replacement in the upper extremity using the NinJa database

Satoru Ohashi<sup>1</sup>, Toshihito Mori<sup>1</sup>, Mitsuyasu Iwasawa<sup>1</sup>, Kimio Masuda<sup>1</sup>, Hiroshi Takamura<sup>1</sup>, Toshihiro Matsui<sup>2</sup>, Sakae Tanaka<sup>3</sup>, Shigeto Tohma<sup>4</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Sagamiara National Hospital, National Hospital Organization, <sup>2</sup>Department of Rheumatology, Sagamiara National Hospital, National Hospital Organization, <sup>3</sup>Department of Orthopaedic Surgery, Faculty of Medicine, University of Tokyo, Tokyo, Japan, <sup>4</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamiara Hospital Hospital, National Hospital Organization

Conflict of interest: None

[Objectives] NinJa was used to investigate factors which influence physical function after total joint replacement in the upper extremity. [Methods] We identified 51 patients (50 women, 1 man) for registered with NinJa who underwent total joint replacement in the upper extremity from 2004 to 2008, and who had a 5-year follow-up without any other surgical procedures. The numbers and values of candidate factors were compared between the cases with better mHAQ scores (group B) and the cases with worse mHAQ scores (group W) at the five year follow-up relative to the baseline score. Examined factors included age, disease duration, location of surgery, stage, class, mHAQ, CRP, ESR, PtPainVAS, Pt-GVAS, DrVAS, DAS28, CDAI, and SDAI. [Results] In group B, disease duration was shorter and DAS28, DAS28CRP, CDAI and SDAI were higher than those in group W. The improvement rates of DAS28, DAS-28CRP, CDAI, and SDAI in group B were higher than those in group W postoperatively. [Conclusion] Our results suggest that the effect of total joint replacement in the upper extremity on physical function improvement continues for a mid-term duration even among RA patients with relatively high disease activity when the disease activity is well controlled.

#### W10-2

##### Treatment experience of periprosthetic fracture for RA knee

Takashi Hasegawa<sup>1</sup>, Shu Saito<sup>1</sup>, Takao Ishii<sup>1</sup>, Takanobu Sumino<sup>2</sup>, Gen Suzuki<sup>1</sup>, Manabu Shimizu<sup>3</sup>, Kenkou Yamada<sup>2</sup>, Gouki Kinoshita<sup>1</sup>, Yasuaki Tokuhashi<sup>1</sup>

<sup>1</sup>Nihon University Itabashi Hospital, Tokyo, Japan, <sup>2</sup>Itabashi Medical Association Hospital, <sup>3</sup>Higashimatuayama Municipal Hospital, <sup>4</sup>Nihon University Hospital

Conflict of interest: None

[Objectives] Periprosthetic fracture is important as TKA postoperative complications, The treatment results of the periprosthetic fracture to RA which treated in our hospital this time are reported. [Methods] Objects are eight-example nine knees which produced postoperative peri-

prosthetic fracture among RA case 668 knees which enforced FNK type TKA. Sex is all women, an average of 68 years old and during the RA disease in an average of 27.5 years at the time of TKA enforcement. We examined the period from surgery to fracture onset, fracture classification, treatment and outcome after treatment. [Results] It is an average of 5.5 years during the period from an operation to fracture development of symptoms. The types of a fracture were six femur supracondylar fracture seven knees, a proximal tibia fracture, and a patella fracture. Treatment whereas femur supracondylar fracture, was conservative treatment 4, plate fixed 2, nail 1. Proximal tibia fracture was treated conservatively 1, patella fracture was treated with wiring 1. 6 cases became a carry of recovery of the hospital and the patient was transferred to the walking ability of pre-injury. [Conclusion] In all the cases, there are also no loosening and breakage of the component, and a bone union is obtained, and progress is good.

### W10-3

#### Treatment of Carpal boss

Yoon Soo Kim, Yoshitsugu Tomita  
Hand Care Center, Ota General Hospital

Conflict of interest: None

[Objectives] Carpal boss is a bony protuberance of the hand at the second and third carpometacarpal (CMC) joint. In recent years, excision of the bony protuberance has been a commonly described treatment, because conservative treatment does not always give relief of symptoms. The following study was designed to evaluate the results of treatment on carpal boss. [Methods] Eight patients were diagnosed and treated for carpal boss, in five cases we performance conservative treatment (nonsteroidal anti-inflammatory agents, corticosteroid injection, splint). three patients need surgical treatment excised bony protuberance to the level of normal joint cartilage. The patients were evaluated clinical and radiographic findings, operative findings, and postoperative results. [Results] All patient undergoing conservtive treatment and surgical treatment were pain relief. In operative findings, superficial branch of radial nerve run near the second and third CMC joint. It suggests clinical syptoms. [Conclusion] Symtomatic relief was observed in all patients undergoing surgical treatment. However, we should care the post-operative course, because some patiens had recurrences at the involved site.

### W10-4

#### SAPHO syndrome with lumbar destructive spondylitis. a case report

Taketoshi Yasuda, Kayo Suzuki, Kenta Watanabe, Yoshiharu Kawagiuchi, Hiraku Motomura, Isao Matsushita, Tomoatsu Kimura  
Department of Orthopaedic Surgery, University of Toyama, Toyama, Japan

Conflict of interest: None

[Introduction] SAPHO syndrome has been described diseases that manifest sterile inflammatory bone lesions together with skin eruptions, SAPHO being an acronym for the following conditions: synovitis, acne, pustulosis, hyperostosis, and osteitis. We report a rare case of SAPHO syndrome with lumbar destructive spondylitis. [Case] 51 years old, man. His chief complaints were lumbago and bilateral leg pain. He was treated by MTX, PSL, and infliximab for psoriasis. His neurological disorder showed the L3 cauda equine syndrome. He had acne in a whole body. The findings of sternoclavicular arthritis and sacroiliitis were absent. Lumbar radiography showed the destructive disc space change and the irregularity of the end plate. MRI revealed the lumbar spinal stenosis from L3 to L5. These findings confirmed SAPHO syndrome. We performed the lumbar posterior decompression and fusion. [Discussion] The most common site of the bone lesion in SAPHO syndrome is the precordial regions called articulatio sternoclavicularis, sternocostal joint and the rib cartilage, and the incidence is 65 to 90%. The spine is the second common sites, whose incidence is 32–52%. We report here a rare case of SAPHO syndrome in which the differential diagnosis included pyogenic spondylitis and metastatic spinal tumor.

### W10-5

#### Psoriasis vulgaris with ectopic ossification in the bilateral hip joint and forearm; a case report

Kenkou Yamada<sup>1,2</sup>, Shu Saito<sup>1</sup>, Masayuki Seki<sup>1</sup>, Takao Ishii<sup>1</sup>, Gen Suzuki<sup>1</sup>, Shinsuke Kikuta<sup>1</sup>, Manabu Shimizu<sup>1</sup>, Noboru Oikawa<sup>1</sup>, Gouki Kinoshita<sup>1</sup>, Takashi Hasegawa<sup>1</sup>, Takanobu Sumino<sup>1,2</sup>, Yasuaki Tokuhashi<sup>1</sup>  
<sup>1</sup>Department of Orthopaedic Surgery, Nihon University School of Medicine, Tokyo, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Itabashi Medical Association Hospital, Tokyo, Japan

Conflict of interest: None

[case] A 58-year-old man consulted our department for severe lumbago in May 2013. He took etretinate 30mg regularly for psoriasis vulgaris. Remarkable limitation of motion in the lumbar spine, the bilateral hip joint and the right forearm was found. The patient could not crouch down. On X-ray examination, ectopic ossification was observed on the bilateral hip joint and the bilateral forearm. That was supposed to be side-effect of etretinate. After withdrawal of etretinate and the use of etidronic acid for several month, the progress of the ectopic ossification was not observed. The ectopic ossification of the right hip joint was excised using the anterolateral approach in the left lateral position in May 2014. Impingement between the acetabular rim and the femoral neck was observed in hip flexion. To prevent recurrence of ectopic ossification, we restarted etidronic acid. Recurrence of ectopic was not observed, thus we excised the ectopic ossification of the left hip and the right forearm in July 2014. No recurrence of ectopic ossification has been found over 4 months. [Conclusion] The patient might need total hip arthroplasty in future, we selected the anterolateral approach. Any recurrences are not observed currently, however careful observation is necessary hereafter.

### W10-6

#### Two cases of seronegative rheumatoid arthritis with onset of monoarthritic form

Yasushi Naganuma<sup>1</sup>, Yuya Takakubo<sup>1</sup>, Suran Yang<sup>1</sup>, Hiroharu Oki<sup>1</sup>, Akiko Sasaki<sup>1</sup>, Hokuto Yuki<sup>3</sup>, Yasunobu Tamaki<sup>2</sup>, Kan Sasaki<sup>1</sup>, Michiaki Takagi<sup>1</sup>  
<sup>1</sup>Department of Orthopaedic Surgery, Yamagata University Faculty of Medicine, <sup>2</sup>Yamagata Saisei Hospital, <sup>3</sup>Okitama Public General Hospital

Conflict of interest: None

[Objective] To report about two cases of seronegative rheumatoid arthritis (SNRA) developed with monoarthritis. [Case 1] Forty-four years female complained swelling of left ankle occurred gradually during a year. CRP level was 1.28 mg/dl and both RF and ACPA were negative. Soft tissue tumor was suspected by MRI. In the pathology of resected tissue, no neoplastic lesion was found. Microbial tissue culture was also negative. The diagnosis was SNRA, improvement of swelling of her ankle and decreased CRP level were obtained after medication with methotrexate. [Case 2] Sixty-five years male complained his wrist pain after falling down on skiing. The X-ray photograph of right hand showed multiple cystic lesions of carpal bones. CRP level was within normal limits and both RF and ACPA were negative. In the pathology, synovium was increased. Tissue culture was also negative. He was also diagnosed as SNRA. Destruction of carpal bones was progressed even after application of methotrexate, but it was prevented by etanercept. [Discussion] Both cases did not meet 2010 ACR/EULAR classification criteria for rheumatoid arthritis, but they were diagnosed SNRA because ruled out any other diseases. Pathological findings and tissue culture examinations were very useful to definite diagnosis.

### W11-1

#### Correlation between efficacy of tocilizumab and levels of oxidative stress markers in patients with rheumatoid arthritis: the 52-week analysis

Hiroaki Niiri<sup>1</sup>, Hiroshi Tsukamoto<sup>2</sup>, Yojiro Arinobu<sup>2</sup>, Mitsuteru Akahoshi<sup>2</sup>, Hiroki Mitoma<sup>2</sup>, Kensuke Oryoji<sup>7</sup>, Yasushi Inoue<sup>13</sup>, Takuya Sawabe<sup>6</sup>, Shuji Nagano<sup>8</sup>, Hiroaki Nishizaka<sup>9</sup>, Seiji Yoshizawa<sup>10</sup>, Yoshifumi Tada<sup>4</sup>, Shigeru Yoshizawa<sup>5</sup>, Takeshi Otsuka<sup>14</sup>, Akira Ueda<sup>12</sup>, Hitoshi Nakashima<sup>11</sup>, Takahiko Horiuchi<sup>3</sup>, Koichi Akashi<sup>2</sup>

<sup>1</sup>Clinical Education Center, Kyushu University Hospital, Fukuoka, Japan, <sup>2</sup>Department of Clinical Immunology, Rheumatology and Infectious Dis-

ease, Kyushu University Hospital, Fukuoka, Japan, <sup>3</sup>Division of Rheumatology, Hematology, and Metabolic Diseases, Kyushu University Beppu Hospital, Beppu, Japan, <sup>4</sup>Department of Rheumatology, Faculty of Medicine, Saga University, Saga, Japan, <sup>5</sup>Department of Rheumatology, National Hospital Organization Fukuoka National Hospital, Fukuoka, Japan, <sup>6</sup>Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital, Hiroshima, Japan, <sup>7</sup>The Centre for Rheumatic Diseases, Matsuyama Red Cross Hospital, Ehime, Japan, <sup>8</sup>Center for Rheumatology, Iizuka Hospital, Fukuoka, Japan, <sup>9</sup>Kitakyushu Municipal Medical Center, Kitakyusyu, Japan, <sup>10</sup>Hamanomachi Hospital, Fukuoka, Japan, <sup>11</sup>Division of Nephrology and Rheumatology, Department of Internal Medicine, Faculty of Medicine, Fukuoka University, <sup>12</sup>Department of Internal Medicine, Miyazaki Prefectural Miyazaki Hospital, <sup>13</sup>Department of Rheumatology, Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan, <sup>14</sup>Munakata Medical Association Hospital, Munakata, Japan

Conflict of interest: None

< Objective > Enhanced risk of atherosclerotic cardiovascular (CV) disease is a key feature of rheumatoid arthritis (RA). Oxidative stress is deeply associated with atherosclerosis. In this study we have studied the correlation between efficacy of tocilizumab (TCZ) and levels of oxidative stress markers in RA patients. < Methods > Patients treated with TCZ were prospectively studied with informed consent. Efficacy of TCZ and levels of 8-OHdG and 8-iso-PGF2a in urine were evaluated at baseline and 52 weeks. < Results > Twenty-two out of 52 patients with RA (mean age 63.5 years; mean disease duration 8.5 years; concomitant MTX 50%) were studied at the 52-week analysis. Levels of 8-OHdG and 8-iso-PGF2a in urine were decreased (at baseline, 28.2 ng/mg Cr and 342.2 pg/mg Cr; at 6 months, 24.0 ng/mg Cr and 288.2 pg/mg Cr). DAS28 (ESR) was decreased from 4.5 to 1.6. The rate of DAS28 (ESR) and CDAI remission was 81.8% and 54.5%, respectively. < Conclusions > Efficacy of TCZ correlated with reduced levels of oxidative stress markers in RA patients. This trend was noted in patients cotreated with TCZ and MTX. Whether these findings are associated with obesity, lipid markers and diabetes will be analyzed and presented.

## W11-2

### Optimization of dose interval by measuring serum trough level of biological agents

Yoshinobu Matsuura, Masashi Narazaki, Hideki Yorifuji, Yasuhiro Kato, Masayuki Nishide, Yoshihiro Hishitani, Toru Hirano, Yoshihito Shima, Tetsuji Naka, Toshio Tanaka, Atsushi Ogata, Atsushi Kumanogoh  
Department of Allergy and Rheumatic Diseases, Osaka University School of Medicine, Osaka, Japan

Conflict of interest: Yes

[Objectives] Biological agents have improved the outcome of patients with rheumatoid arthritis (RA). The dosage amount and interval are usually fixed. We examined the relation between disease activity and serum trough level of biological agents. [Methods] RA patients treated with tocilizumab (TCZ) i.v. (n=48) or golimumab (GLM) s.c. (n=19) were registered. By ELISA, we measured the serum trough levels of the biological agents that do not bind to target molecules. [Results] In TCZ or GLM group, 61 or 58 years old, DAS was 1.88 or 2.22, dose interval was 4.5 or 4.1 weeks, respectively. In TCZ group, the mean trough level was 18.0 µg/ml at 4-weeks interval and it reduced to 6.6 µg/ml at 5-weeks. DAS was 1.92 and 1.49, respectively. In GLM group, the mean trough level was 3.49 µg/ml at 4-weeks interval and it reduced to 1.44 µg/ml at 5-weeks. DAS was 2.24 and 2.12, respectively. The dose interval was extended in two cases. In the 1<sup>st</sup> case, the level of GLM decreased from 2.23 µg/ml at 4-weeks to 1.81 µg/ml at 5-weeks, DAS was 1.27 and 1.45. The 2<sup>nd</sup> case the level of TCZ decreased from 5.04 µg/ml at 5-weeks to 4.42 µg/ml at 6-weeks, DAS was 2.04 and 1.48. [Conclusion] The dose interval could be extended, if the patients show remission and keep certain trough levels of biological agents.

## W11-3

### Multivariate analysis of predictive factors for radiographic remission in RA patients treated with Tocilizumab (TCZ)

Koji Takasugi<sup>1</sup>, Misuzu Yamashita<sup>1</sup>, Masamitsu Natsumeda<sup>1</sup>, Kazuhiko

Ezawa<sup>1</sup>, Yoshihisa Nasu<sup>2</sup>, Wataru Yamamoto<sup>3</sup>, Keiichiro Nishida<sup>4</sup>

<sup>1</sup>Department of Internal Medicine, Center of Rheumatology, Kurashiki Sweet Hospital, Kurashiki, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Center of Rheumatology, Kurashiki Sweet Hospital, Kurashiki, Japan, <sup>3</sup>Department of Clinical Information Management, Kurashiki Sweet Hospital, Kurashiki, Japan, <sup>4</sup>Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Conflict of interest: None

[Objectives] Rheumatoid factor (RF) or anti-CCP antibody (ACPA) have been reported not to influence clinical remission of TCZ. Aim of our study is to determine background factors that predict radiographic remission in RA patients treated with TCZ. [Methods] Various background factors of RA patients who initiated TCZ were included as independent variables. Univariate and multivariate analyses (logistic regression) conducted for identifying factors associated with radiographic remission at 1 year after TCZ treatment. [Results] Concomitant use of PSL or MTX, and RF did not affect radiographic remission. ACPA prior to TCZ initiation affected the TCZ radiographic remission at 1 year after TCZ treatment. ROC analysis revealed that ACPA below 26.2 U/ml predicted the TCZ radiographic remission rate at 1 year after TCZ treatment. The TCZ radiographic remission rate of the patients with ACPA over 26.2 U/ml (n = 31) and below 26.2 U/ml (n = 12) prior to TCZ treatment were 22.6% and 58.3% respectively (p = 0.0351). On the other hand, rapid radiographic progression (RRP) rate were 51.6% and 16.7% respectively (p = 0.0464). [Conclusion] Baseline ACPA can be a promising predictive factor for TCZ radiographic remission and RRP at 1 year after TCZ treatment.

## W11-4

### The predictive factor to achieve bio-free clinical remission after tocilizumab treatment in rheumatoid arthritis

Atsushi Noguchi, Shinsuke Yasuda, Michihito Kono, Eri Sugawara, Ryo Hisada, Kazumasa Ohmura, Toshiyuki Hattori, Sanae Shimamura, Ikuma Nakagawa, Haruki Shida, Toshiyuki Watanabe, Yuka Shimizu, Masaru Kato, Kenji Oku, Toshiyuki Bohgaki, Tetsuya Horita, Tatsuya Atsumi  
Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine

Conflict of interest: None

[Objectives] To investigate the predictive factor relating to bio-free clinical remission after tocilizumab (TCZ) treatment in rheumatoid arthritis (RA). [Methods] Among 71 RA patients introduced with TCZ from 2008 to 2012, we included 27 who achieved clinical remission assessed by DAS28-ESR and discontinued TCZ at 52 weeks after induction. We retrospectively analyzed the clinical courses for one year and 6 months after cessation of TCZ. [Results] The mean age at TCZ induction (baseline) was 54.1 years old and the median disease duration was 2.6 (IQR: 1.6 - 4.4) years. All patients were bio-naïve. ACPA, evaluated by anti-cyclic citrullinated peptide antibody, was positive in 18 cases (66 %). Concomitant use of methotrexate was found in 13 cases (48 %). DAS28-ESR (mean ± S.D) at baseline and 52 weeks from baseline was 4.59 ± 0.61 and 1.54 ± 0.64, respectively. In one year and 6 months after cessation of TCZ, bio-free remission was achieved in 8 cases (30%) and 16 cases (59%) maintained clinical remission or low disease activity. Multiple logistic regression analysis revealed ACPA-negative was an independent predictive factor relating to bio-free clinical remission (p = 0.041). [Conclusion] RA patients without ACPA, who achieved clinical remission with TCZ, may discontinue TCZ treatment.

## W11-5

### The 3-year-follow-up results in patients with RA receiving tocilizumab (TCZ) in the prospective observational multicenter cohort 'Michinoku Tocilizumab' study

Yasuhiko Hirabayashi<sup>1,2</sup>, Tomonori Ishii<sup>2</sup>, Tocilizumab Study Group Michinoku<sup>3</sup>

<sup>1</sup>Department of Rheumatology, Hikarigaoka Spellman Hospital, Sendai, Japan, <sup>2</sup>Department of Hematology & Rheumatology, Tohoku University Hospital, Sendai, Japan, <sup>3</sup>Michinoku Tocilizumab Study Group

Conflict of interest: Yes

[Objectives] To evaluate the safety and efficacy of long-term TCZ treatment for RA patients in real clinical practice. [Methods] A total of 724 patients with RA who started TCZ at 34 centers between 1 Apr 2008 and 31 Dec 2010 have been surveyed for 3 years. The clinical efficacy was evaluated by DAS28ESR and Boolean remission rate in 550 patients. Mean patient age was 59.5 years and mean disease duration 9.8 years. Joint damage was assessed by calculating the modified total Sharp score (mTSS) in 50 patients. [Results] Mean DAS28-ESR was 5.1 initially, falling to 2.3 after 1 year and to 2.2 after 3 years. Boolean remission rate was 0.7% initially, increasing to 21.6% after 1 year and to 24.2% after 3 years. Mean change in mTSS was 0.6, 0.1 and 0.0 within the first, second, and third year, respectively. The structural remission rate was 68.8%, 78.6% and 88.9% within the first, second, and third year, respectively. Frequency of adverse events was no more than that for other biologics. If the reason for discontinuation was inadequate response or adverse event, the 1-, 2-, and 3-year persistence rate was 83.4%, 76.6%, and 72.3%, respectively. [Conclusion] In 3-year analysis, TCZ was shown to be highly efficacious, well tolerated, and efficiently halted radiographic progression.

### W11-6

#### Study for 5years' Treatment Adherence of RA with Tocilizumab by means of Registry approach

Yuichiro Yabe<sup>1</sup>, Toshihisa Kojima<sup>2</sup>, Atsushi Kaneko<sup>6</sup>, Yuji Hirano<sup>3</sup>, Yasuhide Kanayama<sup>5</sup>, Nobunori Takahashi<sup>2</sup>, Masatoshi Hayashi<sup>4</sup>, Nobuyuki Asai<sup>2</sup>, Tomonori Kobayakawa<sup>2</sup>, Naoki Ishiguro<sup>2</sup>

<sup>1</sup>Department of Rheumatology, JCHO Tokyo Shinjuku Medical Center, Tokyo, Japan, <sup>2</sup>Department of Orthopaedics and Rheumatology, Nagoya University School of Medicine, Aichi, Japan, <sup>3</sup>Department of Rheumatology, Toyohashi Municipal Hospital, Aichi, Japan, <sup>4</sup>Department of Orthopaedics and Rheumatology, Nagano Red Cross Hospital, Nagano, Japan, <sup>5</sup>Department of Orthopaedics and Rheumatology, Toyota Kousei Hospital, Aichi, Japan, <sup>6</sup>Department of Orthopaedics and Rheumatology, Nagoya Medical Center, Aichi, Japan

Conflict of interest: None

[Objectives] Six years passed from going on market of Tocilizumab (TCZ). Object is study for treatment adherence of RA with TCZ for 5 years by Registry approach. [Methods] 47 RA treated with TCZ from Tsurumi Biologics Communication Registry. Administered from May 2008 to Oct. 2009. Character, as following; Bio-Naïve were 32%, average MTX dose 7mg/week, average DAS28ESR (4) 5.78±0.94. We figured out treatment adherence of 47cases 5 years after, compared Bio-Naïve and Bio-experienced group, checked reason for quit. Reason, Moving, should be avoided, and figure out treatment adherence except for moving. [Results] Treatment adherence of 47cases 5 years was 45%(21continued/47cases), 43% from Bio-naïve (6/14), 45% from Bio-experienced (15/33). Reason for quit, as following. Moving 12cases, Adverse event 6 (bleeding tendency, auto-immune hepatitis, gastritis, heart failure, NTM, cardiac tumor). Insufficient effect 4, and Natural death, surgery event, pregnancy, remission, each case was one. Avoid reason moving. Treatment adherence of 35cases 5 years, was 60%, 55% from Bio-naïve, 63% from Bio-experienced. [Conclusion] Treatment adherence, 5 years after 1<sup>st</sup> administration of TCZ, was 45%. Avoid moving. Treatment adherence was 60%.

### W12-1

#### Analysis of the effect of tocilizumab (TCZ) after etanercept (ETN): the influence of increasing of the dosage of prednisolone (PSL)

Satoshi Ito<sup>1</sup>, Daisuke Kobayashi<sup>1,2</sup>, Satoru Kodama<sup>1,3</sup>, Tomo Oyakawa<sup>1,4</sup>, Kengo Harigane<sup>1,5</sup>, Asami Abe<sup>1</sup>, Hiroshi Otani<sup>1</sup>, Hajime Ishikawa<sup>1</sup>, Akira Murasawa<sup>1</sup>, Ichiei Narita<sup>2</sup>, Kiyoshi Nakazono<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Niigata Rheumatic Center, <sup>2</sup>Division of Clinical Nephrology and Rheumatology Niigata University Graduate School of Medical and Dental Sciences, <sup>3</sup>Division of Metabolism and Biosystemic Science, Department of Medicine, Asahikawa Medical University, <sup>4</sup>Department of Orthopedic Surgery, University of the Ryukyus, <sup>5</sup>Department of Orthopedic Surgery, Yokohama City University

Conflict of interest: Yes

[Objectives] To clarify the effect of TCZ and PSL after ETN. [Methods] We analyzed 8 patients whose PSL were increased at the switching (group 1) and other 18 patients (group 2). Clinical parameters were compared 4W before to 24W after switching. [Results] 4W before switching, ESR in group 1 was significantly higher than that in group 2 (77.3±22.9 vs 47.1±22.7 mm/hr, p=0.019). At 0W, TJC, ESR, and RF in group 1 were significantly higher than those in group 2 (5.75±4.27 vs 3.33±3.01, 82.2±29.2 vs 47.2±20.5 mm/hr, 674.2±707.4 vs 209.5±133.5 IU/ml, p=0.038, 0.024, 0.033). At 0W, there was no difference in PSL (6.69±4.02 vs 5.25±2.41mg/day). In group 1, 2 patients discontinued TCZ (due to infection and vasculitis). One patient in group 2 discontinued TCZ due to lack of efficacy. At 24W, differences in TJC, ESR, RF in both groups disappeared and PSL were reduced to the same level (3.58±1.63 vs 3.45±2.19 mg/day). In comparison of 0 and 24 W, TJC, DAS28-ESR, ESR, CRP were significantly improved in group 1. In group 2, PSL and MTX were significantly reduced, and DAS28-ESR, patient's VAS, ESR, CRP were significantly improved. [Conclusion] Switching from ETN to TCZ was effective. Transient dose up of PSL was effective in patients with high disease activity.

### W12-2

#### Investigation of the validity of Tocilizumab to invalid patients of anti-TNF inhibitory biologics's treatment. ~2nd report

Noboru Kitamura, Hidetaka Shiraiwa, Takamasa Nozaki, Natsumi Ikumi, Kaita Sugiyama, Yosuke Nagasawa, Hiroki Karasawa, Hirotake Inomata, Atsuma Nishiwaki, Hitomi Haraoka, Mitsuhiro Iwata, Yoshihiro Matsukawa, Masami Takei

Division of Hematology and Rheumatology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

Conflict of interest: Yes

[Background] It is not clear whether other treatment is more effective about switching of treatment to invalidity case of biologics therapy. Now, we report the effectiveness of tocilizumab (TCZ). [Objectives] It was registered at the patient who was not improved even if it treats by anti-TNF therapy. [Methods] We investigated the patient who administered TCZ (8mg/kg/month, div or 162mg/biweekly, SC). 24 weeks after, it was analyzed at disease activity, MMP-3 and mHAQ. [Results] The number of cases was 24 patients (male; 3, female; 24) and mean disease period was 7.8 year. Mean DAS 28 (ESR) was 4.9. Uses of past biologics were infliximab (9), etanercept (9), adalimumab (6). After 24 weeks, DAS28 (ESR), mHAQ and MMP-3 were significantly improved. There was no significant difference between intravenous infusion and subcutaneous infusion. TNF mAbs (infliximab, adalimumab) improved disease activity from early time compared with etanercept. [Conclusion] It was suggested that TCZ was effective therapy against invalid patients of anti-TNF inhibitory biologics's treatment. Especially, TNF mAbs improved disease activity from early time. It was suggested that the further examination will be proposed from now on

### W12-3

#### The outcome of tocilizumab treatment with achievement of glucocorticoids withdrawal against rheumatoid arthritis for 24 months from TBC Registry

Koji Funahashi<sup>1</sup>, Toshihisa Kojima<sup>1</sup>, Nobunori Takahashi<sup>1</sup>, Shuji Asai<sup>1</sup>, Yutaka Yoshioka<sup>1</sup>, Toki Takemoto<sup>1</sup>, Kenya Terabe<sup>1</sup>, Nobuyuki Asai<sup>1</sup>, Yuichiro Yabe<sup>2</sup>, Atsushi Kaneko<sup>3</sup>, Daihei Kida<sup>3</sup>, Yuji Hirano<sup>4</sup>, Seiji Tsuboi<sup>5</sup>, Tomone Shioura<sup>5</sup>, Takayoshi Fujibayashi<sup>6</sup>, Masatoshi Hayashi<sup>7</sup>, Takefumi Kato<sup>8</sup>, Kiwamu Saito<sup>9</sup>, Naoki Ishiguro<sup>1</sup>

<sup>1</sup>Nagoya University Hospital, <sup>2</sup>Japan Community Healthcare Organization Tokyo Shinjuku Medical Center, <sup>3</sup>Nagoya Medical Center, <sup>4</sup>Toyohashi Municipal Hospital, <sup>5</sup>Shizuoka Kosei Hospital, <sup>6</sup>Konon Kosei Hospital, <sup>7</sup>Nagano Red Cross Hospital, <sup>8</sup>Kato Clinic, <sup>9</sup>Saito Clinic

Conflict of interest: Yes

[Objectives] To assess treatment outcome reducing glucocorticoids (GCs) in accordance with EULAR recommendation 2013 with Tocilizumab (TCZ) treatment for 24 months by using Tsurumi Biologics Commu-

nication Registry (TBCR). [Methods] 276 patients with RA have been registered into TBCR as TCZ users were included in this study. We compared three groups which are TCZ treatment without GCs at the baseline (n=95), with stopping GCs by 24 months (n=78) and with persistence of GCs (n=103). We assessed disease activity with DAS28ESR, retention rate of drug continuity with Kaplan-Meier method for 24 months [Results] In GCs (-) group, GCs withdrawal group and GCs continuation group, the values of DAS28ESR at the baseline were 5.39, 5.57, 5.77, respectively. The continuation rate of TCZ treatment associated with inadequate response (IR) and adverse events (AEs) was significant difference between GCs withdrawal group and GCs continuation group (Log-rank test: p=0.007; IR p=0.006; AEs). The 24 months continuation rate associated with IR is 88.0, 95.8, 82.6% in each group. The proportion of achievement with low disease activity and remission with DAS28ESR is 65.4, 67.1, 45.1% in each group. [Conclusion] We confirmed that the good outcome of TCZ treatment with stopping GCs with effectiveness and safety.

#### W12-4

##### The recent trend in description of first biological agents from Turumai Biologics Committee Registry (TBCR)

Yoshikazu Ogawa, Toshihisa Kojima, Nobunori Takahashi, Koji Funahashi, Shuji Asai, Toki Takemoto, Kenya Terabe, Yutaka Yoshioka, Nobuyuki Asai, Tatsuo Watanabe, Takuya Matsumoto, Tomonori Kobayakawa, Naoki Ishiguro  
Department of Orthopaedic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

Conflict of interest: Yes

[Objectives] Seven biological agents are available at present; however, which one to be selected is controversial. We analyzed a recent trend in prescription of first biological agents. [Methods] Using a database from Turumai Biologics Committee Registry (TBCR) from January 2010 to March 2013, we compared the ratio of each biological prescription in the year of 2010, 2011 (n = 526) and 2012, 2013 (n = 291). Seven biological agents were classified into 3 categories, anti-TNF (TNF), Abatacept (ABT) and Tocilizumab (TCZ). [Results] The prescription ratio of TNF/ABT/TCZ were 78.9/16.5/4.6% in 2010 and 2011, 60.8/26.8/12.4% in 2012 and 2013 respectively, TNF decreasing, while ABT and TCZ increasing significantly (p<0.01). In patients with concomitant MTX, 83.1/13.5/3.4% in 2010 and 2011 (n=319), 72.3/15.3/12.4% in 2012 and 2013 (n=202), TNF decreasing, while TCZ increasing significantly (p<0.01). [Conclusion] As a whole and in the concomitant MTX cases where TNF had monopolized the share of biological description so far, the ratio of TNF were proved to be decreasing, suggesting that the position of non-TNF biological agents is growing as first biologics.

#### W12-5

##### The baseline characteristics of Tocilizumab and Abatacept compared to TNF inhibitors from the database of Tsurumai biologic communication registry

Yasumori Sobue<sup>1</sup>, Nobunori Takahashi<sup>1</sup>, Yuichiro Yabe<sup>2</sup>, Takeshi Oguchi<sup>3</sup>, Atsushi Kaneko<sup>4</sup>, Daihei Kida<sup>4</sup>, Yuji Hirano<sup>5</sup>, Koji Funahashi<sup>1</sup>, Shuji Asai<sup>1</sup>, Yutaka Yoshioka<sup>1</sup>, Kenya Terabe<sup>1</sup>, Toki Takemoto<sup>1</sup>, Nobuyuki Asai<sup>1</sup>, Toshihisa Kojima<sup>1</sup>, Naoki Ishiguro<sup>1</sup>

<sup>1</sup>Nagoya University Hospital, Nagoya, Japan, <sup>2</sup>Japan Community Healthcare Organization Tokyo Shinjuku Medical Center, Tokyo, Japan, <sup>3</sup>Anjo Kosei Hospital, Aichi, Japan, <sup>4</sup>National Hospital Organization Nagoya Medical Center, Nagoya, Japan, <sup>5</sup>Toyouhashi Municipal Hospital, Aichi, Japan

Conflict of interest: Yes

[Objectives] We compared the baseline characteristics of RA patients who started biologic agents therapy from the database of Tsurumai biologic communication registry (TBCR) and demonstrated the tendency to choose biologic agents. [Methods] There were 404 cases who started or changed biologic agents from 2012 to 2013. We divided them into the TNF inhibitors group (TNF, n=224), the Tocilizumab group (TCZ, n=72) and the Abatacept group (ABT, n=108), and analyzed the baseline characteristics of TCZ and ABT compared to TNF. [Results] The mean age

was 56.9/60.1/66.1years (TNF/TCZ/ABT). The RA duration was 8.7/10.5/12.4years. The DAS28-ESR score was 4.8/5.0/5.3. The proportion of patients with MTX therapy was 82.5/64.7/43.6%. The proportion of switch patients was 20.5/40.3/27.8%. Compared to TNF, TCZ was statistically chosen for more switch patients. And the proportion of concomitant MTX therapy was lower (p<0.05). ABT was statistically chosen for patients who had older age, longer duration, the lower proportion of concomitant MTX therapy and higher disease activity (p<0.05). In summary ABT was chosen for difficult patients to treat. [Conclusion] It is suggested that patient baseline characteristics influence the tendency to choose TCZ or ABT.

#### W12-6

##### Early effects of tocilizumab or abatacept on bone metabolism in rheumatoid arthritis

Masayasu Kitano<sup>1</sup>, Sachie Kitano<sup>1</sup>, Takeo Abe<sup>1</sup>, Chie Ogita<sup>1</sup>, Yuichi Yokoyama<sup>1</sup>, Tetsuya Furukawa<sup>1</sup>, Takahiro Yoshikawa<sup>1</sup>, Takuya Hino<sup>1</sup>, Atsushi Saito<sup>1</sup>, Aki Nishioka<sup>1</sup>, Masahiro Sekiguchi<sup>1</sup>, Sachi Tsunemi<sup>2</sup>, Naoto Azuma<sup>1</sup>, Naoaki Hashimoto<sup>3</sup>, Shinichiro Tsunoda<sup>1</sup>, Kiyoshi Matsui<sup>1</sup>, Tsuyoshi Iwasaki<sup>2</sup>, Hajime Sano<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan, <sup>2</sup>Department of Pharmacy, Hyogo University of Health Science, Hyogo, Japan, <sup>3</sup>Hashimoto Rheumatology Clinic

Conflict of interest: Yes

[Objectives] To clarify the mechanism of Tocilizumab (TCZ) or Abatacept (ABT) for bone metabolism in rheumatoid arthritis (RA). [Methods] 36 female patients with active RA were started on treatment with TCZ or ABT intravenously. Patient's background between TCZ group (n=19) and ABT group (n=17) was matched. Circulating levels of NTx, osteocalcin (OC), soluble RANKL, osteoprotegerin (OPG), DKK-1, TRACP-5b and osteopontin (OPN) were examined at baseline and after 12 weeks. [Results] In TCZ group, average of NTx, sRANKL, sRANKL/OPG, DKK-1 and OPN levels at 12 weeks decreased significantly from the baseline. Average of OC levels at 12 weeks increased significantly from the baseline. In ABT group, similarly, average of NTx levels tend to decrease and OC levels tend to increase. However, these change were not significant. Average of OPN levels decreased significantly from the baseline and %change of OPN were significantly correlated with %change of NTx. Moreover, %change of NTx were significantly correlated with the baseline of TRACP-5b levels. [Conclusion] These results indicate that TCZ has improved the bone metabolism of RA via the control of RANKL, OPN and DKK-1. In ABT, it is suggested that the bone resorption control mechanism which does not pass control of RANKL exists.

#### W13-1

##### NinJa, a Japanese rheumatoid arthritis database, demonstrated that the size and number of swollen joints correlated with increased systemic inflammation markers. Digital joint swelling showed only trace increases of serum C-reactive protein and erythrocyte sedimentation rate

Kota Shimada<sup>1,4</sup>, Akiko Komiya<sup>2,4</sup>, Naonori Tsuda<sup>1,4</sup>, Kae Onishi<sup>1,4</sup>, Takayasu Kise<sup>1,4</sup>, Yuji Miyoshi<sup>1,4</sup>, Satoshi Watanuki<sup>1,4</sup>, Yoshiki Nagai<sup>1,4</sup>, Eigo Kikuchi<sup>1,4</sup>, Takahiro Nunokawa<sup>1,4</sup>, Toshioki Sawaki<sup>1,4</sup>, Naoto Yokogawa<sup>1,4</sup>, Shoji Sugii<sup>1,4</sup>, Shigeto Tohma<sup>3,4</sup>

<sup>1</sup>Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, Fuchu, Tokyo, Japan, <sup>2</sup>Department of Clinical Laboratory, Sagami National Hospital, National Hospital Organization, Sagami, Kanagawa, Japan, <sup>3</sup>Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami National Hospital, Sagami, Japan, <sup>4</sup>NinJa (National Database of Rheumatic Diseases by iR-net in Japan)

Conflict of interest: None

[Objectives] Few studies have addressed the size of swollen joints (SJs) in evaluating systemic inflammation of RA. We herein examined the correlation between the size of SJs with systemic inflammation markers. [Methods] RA patient (pt) data registered to the *NinJa* database in

2012 were used. Sixty-six joints were classified into 3 size categories, namely, the digital joint (DIPJ, PIP/IPJ, MCP/MTPJ) as a small, the knee as a large, and the others as medium-sized joints. Pts with SJs limited to the 1 joint-size category were grouped by SJ count and compared with cases without SJ. 8446 cases were analyzed. Pts receiving anti-IL-6 or JAK-inhibiting therapies were excluded. **[Results]** Pts with larger numbers of SJs tended to show higher levels of both serum CRP and ESR in each joint-size category. In the medium-sized, or knee joint group, these levels were significantly higher than in the no-swelling group and small joint group with the same SJ count. Linear regression analysis revealed increments of CRP (mg/L) (ESR (mm/1h)) per SJ as 4.6 (8.9) in the knee, 2.4 (5.0) in medium-sized joints, and 0.56 (0.89) in the small joints. **[Conclusion]** The strength of swelling in the joints affecting systemic inflammation marker increased with the involvement of larger and/or more numerous joints.

### W13-2

#### Association of soluble PAD4 and anti-PAD4 antibodies with different ACPA and HLA-DR shared epitope in rheumatoid arthritis

Naoto Umeda, Isao Matsumoto, Asuka Inoue, Yuki Tanaka, Yuko Kurashima, Hoshimi Kawaguchi, Hiroshi Ebe, Yuya Kondo, Hiroto Tsuboi, Hiroshi Ogishima, Takeshi Suzuki, Takayuki Sumida  
Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

Conflict of interest: None

**[Objectives]** To investigate PAD4 and anti-PAD4 Abs, and to clarify the association to ACPA and shared epitope (SE) in RA. **[Methods]** PAD4 and anti-PAD4 Abs were measured by sandwich ELISA using serum or plasma. Samples were obtained from RA (n=148), SLE (n=36), SS (n=37) and HC (n=40). Anti-CCG-2, -7, -CEP-1 and -CCP Abs were measured by ELISA. PAD4 and anti-PAD4 Abs were compared with these ACPA. 2) Patients with RA were genotyped for HLA-DRB1. PAD4 and anti-PAD4 Abs were compared with SE. **[Results]** 1) PAD4 (U/ml) were 111.9 in RA, 30.4 in SLE, 81.9 in SS and 46.6 in HC. PAD4 were significantly higher in RA compared with SLE and HC. Anti-PAD4 Abs were detected in 29.7% patients with RA, whereas they were never detected in SLE, SS and HC. PAD4 in anti-PAD4 positive group (20.7U/ml) were significantly lower in anti-PAD4 negative group (111.9U/ml). PAD4 were not correlated with ACPA. ACPA were significantly higher in anti-PAD4 positive group compared with in negative group. 2) 68.3% of patients had SE. PAD4 was not significant higher in SE positive group. Correlation between positivity of anti-PAD4 Abs and presence of SE was not significant. **[Conclusion]** Soluble PAD4 were higher in RA than in SLE and HC. The anti-PAD4 Abs appeared specifically in RA and could be associated with ACPA.

### W13-3

#### Clinical utility of the new parameter, reticulocyte hemoglobin equivalent (RET-He) in the diagnosis of iron-deficiency state in rheumatoid arthritis (RA) patients

Akikatsu Nakashima<sup>1</sup>, Shunsuke Tsuge<sup>1</sup>, Ichiro Mizushima<sup>1</sup>, Mitsuhiro Kawano<sup>2</sup>

<sup>1</sup>Division of Nephrology and Rheumatology, Ishikawa Prefectural Central Hospital, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine,

Conflict of interest: None

**[Objectives]** The evaluation of iron status in RA patients is difficult. Iron status of the RA patients can be determined by measurement of reticulocyte hemoglobin (Hb) equivalent (RET-He). **[Methods]** We measured complete blood cell counts, RET-He, serum levels of iron, ferritin, unsaturated iron binding capacity (UIBC), CRP among 105 RA patients (21 males and 84 females, mean age 63.3 ±11.8 years). **[Results]** Seven males (33.3%) and 31 females (36.9%) showed anemia (according to WHO criteria; male Hb <13 g/dl, female Hb <12 g/dl). Hb levels were significantly (p<0.01) related with iron, ferritin, TSA, and RET-He levels in our all patients. In female anemic patients, Hb levels were not significantly related with iron, ferritin nor TSA levels, but with significantly with RET-He levels (r=0.392, p<0.05). Even in female anemic patients

with the CRP levels of greater or equal 0.1 mg/dl, this significant relation (r=0.500, p<0.05) was found. **[Conclusion]** RET-He may reflect iron status of anemia more accurately among RA patients than the routine laboratory markers levels which are influenced by chronic inflammation. Further studies will be required to elucidate the significance of RET-He in anemia among RA patients.

### W13-4

#### The functional abnormality of histone H3 lysine 4 methyltransferases in rheumatoid arthritis synovial fibroblasts

Yasuto Araki<sup>1,2</sup>, Takuma Wada<sup>1,2</sup>, Yoshimi Aizaki<sup>1,2</sup>, Kazuhiro Yokota<sup>1</sup>, Hiroshi Kajiyama<sup>1</sup>, Haruhiko Akiba<sup>1</sup>, Kojiro Sato<sup>1</sup>, Yuji Akiyama<sup>1</sup>, Yoon Taek Kim<sup>3</sup>, Hiromi Oda<sup>3</sup>, Toshihide Mimura<sup>1,2</sup>

<sup>1</sup>Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Saitama, Japan, <sup>2</sup>Project Research Division, Research Center for Genomic Medicine, Saitama Medical University, Saitama, Japan, <sup>3</sup>Department of Orthopaedic Surgery, Faculty of Medicine, Saitama Medical University, Saitama, Japan

Conflict of interest: None

**[Objectives]** Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that is hard to be cured completely. Recent advances have revealed that epigenetic mechanisms such as histone modifications are important regulators in gene transcription. The aim of this study was to examine whether epigenetic dysregulation might lead to synovitis in RA. **[Methods]** The mRNA levels of histone lysine methyltransferases (HKMTs) were investigated after TNF $\alpha$  stimulation in RASFs and osteoarthritis (OA) SFs. The change in matrix metalloproteinase, cathepsin, cytokine and chemokine mRNA levels was examined after TNF $\alpha$  stimulation in HKMTs siRNA-treated RASFs. **[Results]** The mRNA levels of MLL and MLL3, which catalyze the methylation of histone H3 lysine 4 (H3K4) that is associated with gene activation, were significantly higher after TNF $\alpha$  stimulation in RASFs than in OASFs. CXCL10, CXCL11 and CCL5 mRNA levels were repressed with siRNA-mediated silencing of MLL or MLL3 in RASFs. The reduction of MLL via siRNA suppressed CXCL10 and CCL5 after TNF $\alpha$  stimulation in RASFs. MLL and MLL3 may regulate certain chemokine gene expression via the methylation of H3K4. **[Conclusion]** H3K4 methyltransferases are suggested to be involved in arthritogenic properties of RASFs through upregulation of chemokines.

### W13-5

#### Serum protein profiles for patients with rheumatoid arthritis by newly comprehensive proteomics analysis

Atsuko Murota<sup>1</sup>, Katsuya Suzuki<sup>1</sup>, Yoshiaki Kassai<sup>2</sup>, Yuumi Goto<sup>2</sup>, Takahiro Miyazaki<sup>2</sup>, Rimpei Morita<sup>3</sup>, Tsutomu Takeuchi<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, <sup>2</sup>Inflammation Drug Discovery Unit, Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited, Kanagawa, Japan, <sup>3</sup>Department of Microbiology and Immunology, Keio University School of Medicine, Tokyo, Japan

Conflict of interest: Yes

**[Objective]** Although there are many reports of dysregulated serum proteins in RA, measurement technologies to investigate a huge number of these simultaneously and well-sensitively have not been established. We applied newly quantitative proteomics to clarify association between serum proteins and pathogenesis in RA. **[Methods]** Serum proteins in 88 samples (RA (n=28), pSS (n=30) and HC (n=30)) were quantified comprehensively by SOMAscan<sup>TM</sup> and analyzed statistically. **[Results]** 1100 of 1128 quantified proteins were selected as analysis object after quality check. 7 proteins including MMP-3 were validated with conventional assays and highly congruent with the proteomics, certified SOMAscan<sup>TM</sup> a reliable quantitative assay. We screened differentially up- and down-regulated proteins in the three groups, by which 195 proteins were statistically extracted. Among fluctuated 124 proteins in RA compared to HC, 41 proteins were elevated. Enrichment analysis revealed these as complements, acute inflammatory proteins and cytokines and chemokines, indicating serum protein signature in RA. 47 molecules were correlated with DAS28-ESR, including complements, cytokines and MMPs. **[Conclu-**

sion] We identified serum protein profiles in RA and correlation between disease activity and complements.

### W13-6

#### Metabolomic analysis for elucidation of metabolic profile of rheumatoid arthritis and different metabolic changes between biologics

Soshi Takahashi, Jun Saegusa, Takaichi Okano, Sho Sendo, Kengo Akashi, Miwa Nishida, Keisuke Nishimura, Yoshinori Kogata, Goichi Kageyama, Akio Morinobu  
Rheumatology and Clinical Immunology, Kobe University Graduate School of Medicine, Kobe, Japan

Conflict of interest: None

**[Objective]** We examined the characteristics of metabolites in the serum of rheumatoid arthritis (RA) patients and revealed the changes of metabolites by biologics (Bio) treatment. **[Methods]** We collected the fasting serum of RA patients who needed starting Bio treatment or switching Bio because of increasing disease activity despite of receiving the oral DMARDs or Bio. 28 patients were included (TNF- $\alpha$  inhibitors (TNF- $\alpha$ i) 13, tocilizumab (TCZ) 7, abatacept (ABT) 8). Non-responder was 3 in TNF- $\alpha$ i and 1 in ABT. We used the fasting serum of 12 healthy controls (HC). We performed metabolomic analysis using a Gas Chromatograph Mass Spectrometer (GCMS-QP2010 Ultra). **[Result]** We detected 99 metabolites from the serum. Comparing the before Bio treatment and HC, there were significant differences in the 44 metabolites, and was clearly difference in the principal component analysis. Several metabolites were significant differences between the before and after the treatment. In the multivariate analysis in responder group of ABT, abnormal metabolic profiles seen in RA were found to approach the metabolic profile of the HC by the treatment. **[Conclusion]** The serum metabolomic analysis may lead to the new diagnostic methods for RA and the identification of biomarkers useful in the proper use of Bio.

### W14-1

#### Comprehensive analysis of peripheral blood phenotype in patient with rheumatoid arthritis

Masaru Takeshita<sup>1</sup>, Katsuya Suzuki<sup>1</sup>, Yoshiaki Kassai<sup>2</sup>, Takahiro Miyazaki<sup>2</sup>, Tsutomu Takeuchi<sup>1</sup>  
<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, <sup>2</sup>Inflammation Drug Discovery Unit, Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited, Kanagawa, Japan

Conflict of interest: Yes

**[Objectives]** Previous reports showed Th1, Th17, Tfh, and Breg were related to activity of rheumatoid arthritis (RA), but results were sometimes fragmental and inconsistent due to differences of patients' background and analysis methods. The purpose of this study is to elucidate the most related subset to RA pathophysiology. **[Methods]** Peripheral blood samples from 34 untreated RA, 53 healthy controls (HC), and 60 Sjogren's syndrome (SjS) were analyzed comprehensively by FACS. MTX monotherapy group further chased the change of phenotype with treatment. These data were statistically analyzed with clinical information. **[Results]** The proportion of memory T cell and naive B cell increased, and the proportion of DC decreased in both RA and SjS. CD4/8 ratio of T cell was increased only in RA. RA disease activity was correlated to Th17 and Plasma blast positively, and to Breg negatively. Th17 and Breg were also negatively correlated only in RA. Breg in RA was reported to have poor inhibitory effect to Th17 differentiation in vitro, and our results confirmed Breg-Th17 axis in vivo. By the MTX treatment, many subsets including Th17, Plasma Blast, and Breg, were decreased. **[Conclusion]** Decrease of Breg and increase of Th17 might be mutually related and participated in the pathophysiology of RA.

### W14-2

#### New classification of helper T (Th) cells by cell surface markers and analysis of their function in rheumatoid arthritis (RA) patients

Shunta Kaneko, Yuya Kondo, Masahiro Tahara, Masahiro Yokosawa, Seiji Segawa, Hiroto Tsuboi, Isao Matsumoto, Takayuki Sumida

Department of Internal Medicine, Faculty of Medicine, University of Tsukuba

Conflict of interest: None

**[Objective]** The purpose of this study is to classify Th subsets by cell surface markers and analysis of their function in the pathogenesis of RA. **[Methods]** We collected peripheral blood mononuclear cells (PBMC) of healthy control (HC) and RA patients. CD4<sup>+</sup>T cells were isolated from PBMC by magnetic cell sorting, and were analyzed by flow cytometry as follows. 1) In HC, the expression of transcription factors such as T-bet and ROR $\gamma$ t were examined in each Th subsets classified from the expression of cell surface antigens (CD45RA, CXCR5, CXCR3, CCR6). 2) The proportion of Th subsets and the expression of transcription factors were analyzed in HC and RA patients. **[Results]** 1) CD45RA-CXCR5-CXCR3+CCR6-cells (Th1) and CD45RA-CXCR5-CXCR3-CCR6+c cells (Th17) significantly expressed T-bet and ROR $\gamma$ t, respectively. 2) In RA patients, CD45RA-CXCR5-CXCR3-CCR6-cells (Th2) were significantly increased and CD45RA-CXCR5-CXCR3+CCR6+c cells (Th1/Th17) were significantly decreased in comparison with HC. **[Conclusion]** In RA patients, CD45RA-CXCR5-CXCR3-CCR6-cells (Th2) were significantly increased relative to HC, suggesting that these Th cells are related with the pathogenesis of RA.

### W14-3

#### Distribution and pathological relevance of peripheral blood Th22 cells in rheumatoid arthritis (RA)

Yusuke Miyazaki<sup>1</sup>, Shingo Nakayamada<sup>1</sup>, Satoshi Kubo<sup>1</sup>, Kei Sakata<sup>2</sup>, Kaoru Yamagata<sup>1</sup>, Kazuhisa Nakano<sup>1</sup>, Ippei Miyagawa<sup>1</sup>, Naoki Yunoue<sup>1</sup>, Maiko Yoshikawa<sup>1</sup>, Yoshiya Tanaka<sup>1</sup>

<sup>1</sup>First Department of Internal Medicine, University of Occupational and Environmental Health, School of Medicine, Kitakyushu, Fukuoka, Japan, <sup>2</sup>Mitsubishi Tanabe Pharma Corporation

Conflict of interest: None

**Objectives.** Although elevated levels of IL-22 in RA synovial fluids were reported, pathological roles of IL-22 remain unclear. Th22 cells have been identified as a new subset which secretes IL-22. We examined the frequencies of peripheral Th22 cells in a correlation with clinical findings. **Methods.** Twenty-eight patients with active RA and 5 healthy controls (HC) were analyzed. Circulating Th22 cells (CD3<sup>+</sup>CD4<sup>+</sup>CCR4<sup>+</sup>CCR6<sup>+</sup>CCR10<sup>+</sup>) were analyzed by flow cytometry. **Results.** The proportion of Th22 cells was decreased in active RA compared to HC ( $p=0.04$ ). By contrast, the proportion of activated Th22 was increased in active RA ( $p<0.01$ ). There was positive correlation between percentage of activated Tfh cells and ACPA levels, whereas negative correlation was found between activated Th22 cells and ACPA levels ( $p=0.05$ ). **Conclusions.** The percentage of Th22 cells decreased but activated Th22 cells increased, and negative correlation between activated Th22 cells and ACPA were observed in highly active RA. The results may suggest that Th22 cells which co-express chemokine receptors CCR4, CCR6 and CCR10 can accumulate into inflamed synovial tissues where the ligands such as CCL20 are highly expressed, and were related to pathogenesis independent of the autoantibody production.

### W14-4

#### Local proliferation but not migration from other sources is responsible for synovial fibroblast accumulation in a murine model of rheumatoid arthritis

Yusuke Matsuo<sup>1,2</sup>, Kimito Kawahata<sup>1</sup>, Fumitaka Mizoguchi<sup>1,2</sup>, Tetsuya Saito<sup>1,2</sup>, Nobuyuki Miyasaka<sup>1</sup>, Hitoshi Kohsaka<sup>1,2</sup>

<sup>1</sup>Department of Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, <sup>2</sup>Japan Science and Technology Agency, Core Research for Evolutional Science and Technology

Conflict of interest: None

**[Objectives]** Rheumatoid arthritis (RA) is characterized by destructive synovial hyperplasia that results from increased numbers of synovial fibroblasts (SF). The mechanisms to increase SF should be new therapeutic

tic targets while current therapies that regulate inflammation have problems in efficacy and safety. However, little is known about the mechanisms. In particular, migration accounts in other fibrosis. The aim of this study is to clarify whether SF migrate from other sources or proliferate locally in arthritis. [Methods] SF were identified using collagen type I alpha 2 reporter mice (Col1a2-GFP). To examine migration from other sources, collagen antibody-induced arthritis (CAIA) was induced after bone marrow transplantation and parabiosis. Proliferation was evaluated by staining of Ki67 in Col1a2-GFP and geminin that indicates S/G2/M-phase of cell cycle in fluorescent ubiquitination-based cell cycle indicator transgenic mice. [Results] No GFP<sup>+</sup> SF was observed in the transplanted and parabiosed wild-type mice with CAIA. The number of Ki67<sup>+</sup> SF and geminin<sup>+</sup> SF increased in CAIA. [Conclusion] SF accumulate by local proliferation but not by migration from other sources in CAIA. Inhibition of local proliferation of SF should be a promising therapeutic strategy in RA.

#### W14-5

##### Enhanced Osteoclastogenesis in iPS cell-derived monocytes from Rheumatoid arthritis patient

Mari N Ito<sup>1,2</sup>, Miho Murakami<sup>1,2</sup>, Norihiro Nishimoto<sup>1,2</sup>

<sup>1</sup>Department of Molecular Regulation for Intractable Diseases, Institute of Medical Science, Tokyo Medical University, <sup>2</sup>Osaka Rheumatology Clinic

Conflict of interest: None

[Background and Objective] Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic proliferation of synovial cells and destructive polyarthritis. It is reported that the inflammatory cytokines stimulate osteoclastogenesis in the affected joints. However, it remains unclear whether genetic factors influence the osteoclastogenesis in RA. To answer this question, we compare the osteoclastogenesis of monocytes derived from induced pluripotent stem cells (iPS) cells of RA patients and their non-onset family members (NORs). [Methods] First, we induced monocytes from the iPS cells of RA patients and NORs. CD14<sup>+</sup> cells were isolated and cultured on glass chamber slides with M-CSF and RANKL. After 8 days of culture, the numbers of TRAP-positive cells on the slide were counted microscopically. The levels of fluorescent labelled chondroitin sulfate were measured for the bone resorption activities. [Results] The numbers of TRAP-positive cells derived from RA-iPS cells and NOR-iPS cells were 430±87 and 90±7, respectively. The fluorescent intensity of chondroitin sulfate produced by osteoclasts from RA-iPS cells and NOR-iPS cells were 4869±838 and 954±252, respectively. [Conclusions] Our results indicate that enhancement of osteoclastogenesis in RA depends on genetic factors.

#### W14-6

##### Possible role of Fibroblast-Like Synoviocytes in osteogenesis inhibition

Satoshi Yamasaki, Takaki Nojima, Yusuke Yoshida, Kazuhiko Kumagai, Eiji Sugiyama

Department of Clinical Immunology and Rheumatology, Hiroshima University Hospital

Conflict of interest: None

[Objectives] Bone erosion is a hallmark of rheumatoid arthritis (RA). Activation of osteoclast plays important role in cortical bone destruction. Osteoblast inactivation was reported in arthritis model mouse. Wnt family proteins are thought to promote osteogenesis via activation of  $\beta$ -catenin in association with TCF, which is blocked by DKK-1 or SOST. Fibroblast-like synoviocyte (FLS) is a unique articular resident cell and is activated in RA. In this study, we examine whether FLS produce DKK-1 to inhibit Wnt signaling. [Methods] DKK-1 expressions in synovial tissue were examined by immunostaining. DKK-1 productions from cultured FLS were measured by ELISA. mRNA expression was quantified by SYBR Green real-time PCR. Activity of  $\beta$ -catenin pathway was monitored by luciferase assay using TCF reporter plasmid. Anti DKK-1 antibodies were used to neutralize DKK-1. [Results] FLS produce DKK-1. FLS supernatant inhibited the *RUNX2*, *COL1A1* mRNA in MSC and Wnt3a induced luciferase activity of TCF reporter was significantly inhibited,

which was blocked by addition of anti DKK-1 neutralizing antibodies. [Conclusion] It is suggested that FLS produce DKK-1 to inhibit osteogenesis in RA. Blockade of DKK-1 in RA may ameliorate bone destruction.

#### W15-1

##### Relationship between lymphocyte count and risk of infection in Japanese rheumatoid arthritis patients treated with tofacitinib

Yoshiya Tanaka<sup>1</sup>, Tsutomu Takeuchi<sup>2</sup>, Tomohiro Hirose<sup>3</sup>, Shigeyuki Toyozumi<sup>3</sup>, Sriram Krishnaswami<sup>4</sup>, Mark Collinge<sup>4</sup>, Samuel H Zwillich<sup>4</sup>

<sup>1</sup>University of Occupational and Environmental Health Japan, Kitakyushu, Japan, <sup>2</sup>Keio University, Tokyo, Japan, <sup>3</sup>Pfizer Japan Inc, Tokyo, Japan, <sup>4</sup>Pfizer Inc, Groton, CT, USA

Conflict of interest: Yes

[Objectives] To characterize changes in absolute lymphocyte counts (ALC) in patients (pts) from Japanese centers following tofacitinib treatment and evaluate the link between ALC and incidence rate (IR) of infection. [Methods] ALC and adverse event data of herpes zoster (HZ), treated (TI) and serious (SI) infection were analyzed in tofacitinib Phase (P)2, P3 and open-label long-term extension (LTE) RA studies conducted in Japan (April 2014 data cut). Pts received tofacitinib 5 or 10 mg twice daily (P3 and LTE; also 1, 3, and 15 mg twice daily in P2). [Results] Pooled data of 556 pts (1705 pt-yrs) treated with tofacitinib showed mean ALC ( $\times 10^3$  cells/mm<sup>3</sup>) increased from 1.40 at baseline (BL [n=556]) to 1.67 at Month 3 (M3 [n=523]), returned to 1.36 by M18 (n=442), and was lower than BL thereafter (0.99 at M75 [n=3]). Analysis of IR by nadir lymphocyte level deciles showed TI, SI and HZ were higher for pts in the lowest decile (mean nadir lymphocyte count 0.38). 14 pts with confirmed lymphopenia (ALC <0.5) had a TI, SI and/or HZ, though these events were not necessarily synchronized. [Conclusion] Long-term tofacitinib treatment in pts with moderate to severe RA is associated with modest mean decreases in ALC. ALC<0.5 may be a clinically relevant threshold for defining increased risk of SI.

#### W15-2

##### Tofacitinib, an oral Janus kinase inhibitor: analysis of malignancies in Japanese patients across the rheumatoid arthritis clinical program

Yoshiya Tanaka<sup>1</sup>, Tsutomu Takeuchi<sup>2</sup>, Hisashi Yamanaka<sup>3</sup>, Tomohiro Hirose<sup>4</sup>, Shigeyuki Toyozumi<sup>4</sup>, Samuel H Zwillich<sup>5</sup>, Jamie Geier<sup>6</sup>, Lisy Wang<sup>5</sup>

<sup>1</sup>University of Occupational and Environmental Health, Kitakyushu, <sup>2</sup>Keio University, Tokyo, Japan, <sup>3</sup>Tokyo Women's Medical University, Tokyo, Japan, <sup>4</sup>Pfizer Japan Inc, Tokyo, Japan, <sup>5</sup>Pfizer Inc, Groton, CT, USA, <sup>6</sup>Pfizer Inc, New York, NY, USA

Conflict of interest: Yes

[Objectives] To evaluate malignancy events (excluding non-melanoma skin cancer) in patients (pts) from Japanese centers in the tofacitinib rheumatoid arthritis (RA) clinical program. [Methods] Data were pooled from 2 Phase (P) 2, 1 P3 and 1 open-label long-term extension (LTE) RA studies conducted in Japan (April 2014 data cut). Pts received tofacitinib 5 or 10 mg twice daily (P3 and LTE; also 1, 3, and 15 mg twice daily in P2). [Results] 556 pts (1705 pt-yr) received tofacitinib in the P2/P3/LTE studies; 22 pts reported malignancies; the most common were gastric (n=5), breast (n=3) and lung cancer (n=3). Overall incidence rate (IR, pts with events per 100 pt-yr [95% CI]) for all malignancies was 1.29 (0.81, 1.96). Cumulative IR (95% CI) was 0.39 (0.01, 2.19) during Months (M) 0-6, 1.23 (0.45, 2.67) during M 0-12 and was then stable over 54 months. [Conclusion] In Japanese pts in the tofacitinib RA clinical development program, gastric, breast and lung cancer were most common. These malignancies are also common in the general Japanese population. IRs appear similar to the global RA tofacitinib population (1). Further monitoring in the clinical practice setting is warranted to evaluate risk of malignancy. Reference: 1. Winthrop K. et al, Arthritis Rheumatol. 2014; 66 (10):2675-84



### W15-3

#### Relationship between CD16+CD56+ Natural Killer Cell Counts and Infections and Malignancies in Japanese Rheumatoid Arthritis Patients Treated with Tofacitinib

Yoshiya Tanaka<sup>1</sup>, Tsutomu Takeuchi<sup>2</sup>, Tomohiro Hirose<sup>3</sup>, Shigeyuki Toyozumi<sup>3</sup>, Sriram Krishnaswami<sup>4</sup>, Mark Collinge<sup>4</sup>, Samuel H Zwillich<sup>4</sup>  
<sup>1</sup>University of Occupational and Environmental Health, Kitakyushu, Japan, <sup>2</sup>Keio University, Tokyo, Japan, <sup>3</sup>Pfizer Japan Inc, Tokyo, Japan, <sup>4</sup>Pfizer Inc, Groton, CT, USA

Conflict of interest: Yes

[Objectives] To describe the link between CD16+CD56+ natural killer and natural killer T cell counts (NK/NKT CC) and risk of infection and malignancy in patients (pts) from Japanese centers in the tofacitinib RA clinical program. [Methods] Pts from 2 Phase (P)2 and 1 long-term extension studies received tofacitinib 5 or 10 mg BID (also 1, 3, 15 mg BID in P2). Baseline (BL), nadir, and maximum change from BL in NK/NKT CC were divided into quartiles or deciles and incidence rates (IR) of herpes zoster, malignancy excluding non-melanoma skin cancer (M), treated infection and serious (SI) infection calculated. [Results] Tofacitinib treatment led to median (range) change from BL in NK/NKT CC ( $\times 10^3$  cells/mm<sup>3</sup>) of 0.01 (-0.43, 0.54) and -0.01 (-0.45, 0.24) at Month (M) 3 (n=343) and M72 (n=17), respectively. Pts with BL or nadir NK/NKT CC <0.1 showed similar IR for all endpoints compared to pts with BL or nadir NK/NKT CC between 0.1 and 0.4. Pts with high nadir NK/NKT CC (>0.3) had shorter mean treatment exposure and higher IR for SI and M. [Conclusion] Across 4 endpoints, there was no NK/NKT CC threshold below which risk was increased. The apparent increased IR for SI and M at high nadir NK/NKT CC may be confounded by sampling frequency and treatment duration and requires further investigation.

### W15-4

#### Herpes Zoster and Tofacitinib Therapy in Japanese Patients with Rheumatoid Arthritis

Kunihiro Yamaoka<sup>1</sup>, Yoshiya Tanaka<sup>2</sup>, Yosuke Morishima<sup>3</sup>, Shigeyuki Toyozumi<sup>3</sup>, Tomohiro Hirose<sup>3</sup>, Sriram Krishnaswami<sup>4</sup>, Hernan Valdez<sup>5</sup>  
<sup>1</sup>Keio University, Tokyo, Japan, <sup>2</sup>University of Occupational and Environmental Health, Kitakyushu, Japan, <sup>3</sup>Pfizer Japan Inc, Tokyo, Japan, <sup>4</sup>Pfizer Inc, Groton, CT, USA, <sup>5</sup>Pfizer Inc, New York, NY, USA

Conflict of interest: Yes

[Objectives] To describe the risk of Herpes Zoster (HZ) in patients (pts) from Japanese study centers across the tofacitinib rheumatoid arthritis (RA) clinical program. [Methods] HZ adverse events were identified in tofacitinib Phase (P)2, P3 and open-label long-term extension (LTE) RA studies conducted in Japan (April 2014 data cut). Pts received tofacitinib 5 or 10 mg twice daily (P3 and LTE) or 1, 3, 5, 10 or 15 mg twice daily (P2). Exposure-adjusted incidence rates (IRs; pt with events per 100 pt-years [95% CI]) were calculated. [Results] 556 Japanese pts received tofacitinib (1705 pt-yrs exposure). 120 tofacitinib-treated pts experienced 138 HZ events; IR was 8.01 (6.64, 9.57). 19 pts had serious HZ events with an IR of 1.12 (0.67, 1.75). 17 pts with HZ events permanently discontinued study treatment. Most HZ events (n=131; 95%) were mild or moderate in severity; 7 (5%) events were severe. 12 pts (2%) experienced recurrence of HZ ( $\geq 2$  events). IRs by 6-month interval were stable over time. IR was highest in the 60-69 years-of-age bracket. [Conclusion] In Japanese pts treated with tofacitinib, HZ incidence rates were higher than those reported for the global population (1). Most cases were mild or moderate. Reference: 1. Winthrop K. et al, *Arthritis Rheumatol.* 2014;66(10):2675-84

### W15-5

#### Efficacy and safety of a novel disease-modifying antirheumatic drug, iguratimod, as an add-on therapy for patients with rheumatoid arthritis

Daisuke Kobayashi<sup>1,2</sup>, Satoshi Ito<sup>1</sup>, Satoru Kodama<sup>1</sup>, Kengo Harigane<sup>1</sup>, Tomo Oyakawa<sup>1</sup>, Hiroshi Otani<sup>1</sup>, Asami Abe<sup>1</sup>, Hajime Ishikawa<sup>1</sup>, Akira Murasawa<sup>1</sup>, Ichiei Narita<sup>2</sup>, Kiyoshi Nakazono<sup>1</sup>

<sup>1</sup>Niigata Rheumatic Center, <sup>2</sup>Division of Clinical Nephrology and Rheumatology, Graduate School of Medical and Dental Sciences, Niigata Uni-

versity

Conflict of interest: None

[Objectives] We examined the efficacy and safety of iguratimod (IGU). [Methods] RA patients who had been prescribed IGU at our hospital were enrolled. The patients' data were obtained retrospectively from their medical records. Patients involving discontinuation of IGU or treatment intensification were excluded from subsequent data collection. The efficacy of IGU was evaluated at week 12. [Results] One hundred and nine patients received IGU. Nine patients who discontinued taking IGU within one week because of nausea in 3, skin rash in 2, and brain hemorrhage in 1, and eleven patients who received IGU concomitantly with other DMARDs were excluded and the other 89 were enrolled. During the follow-up period, 2 patients required further treatment intensification, and 4 discontinued IGU because of liver injury in 2, pulmonary hemorrhage in 1 and malignant lymphoma in 1. DAS28 (4) ESR improved from 4.27 (3.69-4.94) at the baseline to 3.01 (2.2-3.65) ( $p < 0.001$ , Wilcoxon signed-rank test) at 12 weeks. Furthermore, patients who received less than 3 kinds of DMARDs responded well to IGU (chi-square (1, N=64)=7.33,  $p=0.0068$ ) [Conclusions] IGU is effective for RA patients, and might be more effective for those who have been treated with less than 3 kinds of DMARDs.

### W15-6

#### Therapeutic effect of Iguratimod for the treatment of rheumatoid arthritis

Hirotaaka Yamada, Kenta Misaki, Rintaro Saito, Yuri Nakamura, Yoshie Gon, Takumi Nagamoto, Hisayo Horiuchi, Toshihiko Yokota  
Endocrinology and Rheumatology, Kurashiki Central Hospital, Okayama, Japan

Conflict of interest: None

[Objectives] The aim of this study is to evaluate effectiveness of iguratimod (IGU) for rheumatoid arthritis (RA). [Methods] From January, 2013 to July, 2014, RA patients under the treatment by previous disease-modifying anti-rheumatic drugs (DMARDs) were enrolled. IGU was administered to the patients (25-50mg/day). RA disease activity (DAS28-CRP, SDAI, CDAI) and musculoskeletal ultrasound (MSKUS) estimation was divided into gray scale (GS) (grade 0-3) and power Doppler examination (PD) (grade 0-3) at baseline and week16. [Results] Forty-six patients were enrolled (baseline patient characteristics: median age: 67 years (range: 33-81 years), disease duration: 12.0 years, female: 33 cases (71.7%), mean DAS28-CRP: 3.30 $\pm$ 0.28, SDAI: 14.1 $\pm$ 2.4, CDAI: 13.0 $\pm$ 2.0, respectively). At week 16, DAS28-CRP and CDAI from baseline were significantly decreased. Thirty patients (65.2%) achieved clinical remission (CR) or low disease activity (LDA). MSKUS analysis was performed in 34 patients. PD of MSKUS in week16 was ameliorated compared with those of in baseline (GS: baseline: 2.15 $\pm$ 0.24 vs week 16: 1.97 $\pm$ 0.23 ( $p=0.29$ ), PD: baseline: 2.00 $\pm$ 0.30 vs week 16: 1.51 $\pm$ 0.30 ( $p=0.03$ )). [Conclusion] IGU treatments significantly inhibited the disease activity of RA not only in clinical but also structural improvement in MSKUS.

### W16-1

#### Efficacy and Safety of Iguratimod for Rheumatoid Arthritis

Tsuneo Kondo, Akiko Shibata, Ryota Sakai, Kentaro Chino, Ayumi Okuyama, Hirofumi Takei, Koichi Amano  
Saitama Medical Center, Saitama Medical University

Conflict of interest: None

[Objectives] We evaluate the clinical efficacy and safety of iguratimod (IGU) for RA patients. [Methods] 62 patients who had been treated with IGU and had been followed up for 52 weeks were analyzed. Efficacy and safety were evaluated utilizing clinical and laboratory findings. [Results] The mean age was 61.3 and 75.8% of the patients were female. MTX was used in 46.8%, the average dose was 8.6 mg/week. 21% of the patients had interstitial pneumonia and 6.5% had NTM. LOCF analysis revealed that DAS28-ESR and SDAI decreased significantly from 4.49 to 3.09 and from 18.5 to 7.44 in 24 weeks respectively ( $p < 0.01$ ). The effica-

cy was sustained until 52 weeks (DAS28-ESR 2.98, SDAI 6.98). Remission rate in DAS28-ESR was 33.9% in 24 weeks, 31.8% in 52 weeks. HAQ-DI score also decreased from 1.2 to 0.9 in 52 weeks ( $p < 0.05$ ). The difference between the efficacy of IGU with and without MTX was not significant. 29.0% of the patients discontinued IGU within 52 weeks. The reason of cessation consisted of adverse events (19.3%) and lack of efficacy (4.8%). Adverse events were digestive symptom ( $n=5$ ), liver dysfunction ( $n=3$ ), NTM reactivation ( $n=1$ ). There's no serious adverse events. [Conclusion] IGU was well tolerated and cheap, so it's a new useful option as small molecule DMARDs for RA patients.

### W16-2

#### Influences of disease activity at initiation of iguratimod on efficacy of iguratimod in patients with rheumatoid arthritis from multicenter study (TBCR-plus)

Yuji Hirano<sup>1</sup>, Yasuhide Kanayama<sup>2</sup>, Hiroyasu Kanda<sup>3</sup>, Kiwamu Saito<sup>4</sup>, Takayasu Ito<sup>5</sup>, Shinya Hirabara<sup>1</sup>, Atsushi Kaneko<sup>3</sup>, Toshihisa Kojima<sup>6</sup>, Naoki Ishiguro<sup>6</sup>

<sup>1</sup>Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan, <sup>2</sup>Department of Orthopaedic Surgery and Rheumatology, Toyota Kosei Hospital, Toyota, Japan, <sup>3</sup>Department of Orthopaedic Surgery and Rheumatology, Nagoya Medical Center, Nagoya, Japan, <sup>4</sup>Saito Orthopaedic Surgery and Rheumatology Clinic, Nagoya, Japan, <sup>5</sup>Ito Orthopaedic Surgery Hospital, Nagoya, Japan, <sup>6</sup>Department of Orthopaedic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

Conflict of interest: Yes

[Objectives] To investigate efficacy of iguratimod (IGU) in patients with RA with focus on disease activity (DA) at initiation of IGU. [Methods] Data from multicenter study (TBCR-plus) was used. 65 cases (53 females and 12 males) were included. These patients were divided into two groups (high DA group; HG and moderate and low DA group; MLG) using DAS28-CRP at initiation of IGU. 38 cases were included in HG and 27 cases were included in MLG. Patients' characteristics, time course of disease activity, drug retention rate and change value in DA parameters from 0w to 52w were compared with each other. [Results] MTX use rate was significantly low in HG compared with in MLG (39.5%/66.7%). Mean DAS28-CRP at 0, 4, 8, 12, 24 and 52w was 5.05, 4.40, 4.19, 3.80, 3.52 and 3.33 in HG and 3.26, 3.16, 2.80, 2.49, 2.43 and 2.52 in MLG. DAS28-CRP was significantly decreased in both groups. Same finding was observed in SDAI. Drug retention rates at 52w were 71.1% in HG and 77.9% in MLG. Delta DAS28-CRP from 0w to 52w were 1.73 in HG and 0.74 in MLG ( $p < 0.01$ ). Delta SDAI were 13.8 in HG and 3.3 in MLG ( $p < 0.01$ ). [Conclusion] This study suggests that IGU is one of the options not only in RA patients treated with sufficient MTX but also in RA patients with high DA treated with insufficient MTX.

### W16-3

#### Efficacy of iguratimod plus methotrexate in active rheumatoid arthritis patients with an inadequate response to high-dose methotrexate

Naofumi Chinen<sup>1</sup>, Takayuki Wakabayashi<sup>1</sup>, Noriko Sasaki<sup>2</sup>, Shinichi Nogi<sup>2</sup>, Kiri Honda<sup>2</sup>, Yasushi Koyama<sup>2</sup>, Takayoshi Kurabayashi<sup>2</sup>, Sho Sasaki<sup>2</sup>, Chiho Yamada<sup>2</sup>, Shinji Sato<sup>2</sup>, Yasuo Suzuki<sup>2</sup>

<sup>1</sup>Division of Rheumatology, Tokai University Hachioji Hospital, Tokyo, Japan, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Tokai University School of Medicine, Kanagawa, Japan

Conflict of interest: None

[Objectives] We investigated the efficacy of iguratimod (IGU) plus methotrexate (MTX) in active rheumatoid arthritis (RA) patients with an inadequate response to high-dose MTX. [Methods] Seventeen patients with RA who didn't get remission despite treatment with high-dose MTX over 10mg/week were treated with combination therapy of IGU. [Results] Patients data (mean±standard error) were age 48.2±3.0 years old, disease duration 10.2±2.1 years, stage 2.6±0.4, MTX dosages 12.3±0.6 mg/week, etanercept use 18%( $n=3$ ), prednisolone use 64%( $n=11$ ). IGU dosages at 25mg was 35%( $n=6$ ) and at 50mg was 65%( $n=11$ ). To compared with 0 and 24 week after addition of IGU, DAS28 (ESR) and SDAI were statistically significantly improved at 4.45±0.18 to 2.85±0.30\* and at 15.2±1.2 to 6.1±1.5\*( $P < 0.01$  paired *t*-test). In DAS28 (ESR), remis-

sion and low disease activity were gotten highly rate compared with at 0 week ( $n=14$ , low 7%, moderate 79%, high 14%) and at 24 week ( $n=8$ , remission 25%, low 63%, moderate 12%); same tendency showed in SDAI (from  $n=11$ , low 18%, moderate 82% to  $n=9$ , remission 33%, low 45%, moderate 22%). [Conclusion] Combination therapy with high-dose MTX and IGU was good treatment option in active RA with an inadequate response to high-dose MTX.

### W16-4

#### Clinical efficacy of add-on Igaratimod therapy in patients with rheumatoid arthritis despite of methotrexate ~A MULTICENTER REGISTRY STUDY~

Yasuhide Kanayama<sup>1</sup>, Toshihisa Kojima<sup>2</sup>, Yuji Hirano<sup>3</sup>, Atsushi Kaneko<sup>4</sup>, Nobunori Takahashi<sup>2</sup>, Yutaka Yoshioka<sup>2</sup>, Hiroyasu Kanda<sup>4</sup>, Takefumi Kato<sup>5</sup>, Shinya Hirabara<sup>3</sup>, Naoki Ishiguro<sup>2</sup>

<sup>1</sup>Department of Orthopedic Surgery and Rheumatology, Toyota Kosei Hospital, Toyota, Japan, <sup>2</sup>Department of Orthopedic Surgery and Rheumatology, Nagoya University Graduate School of Medicine, Nagoya, Japan, <sup>3</sup>Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan, <sup>4</sup>Department of Orthopedic Surgery, Nagoya Medical Center, Nagoya, Japan, <sup>5</sup>Department of Orthopedic Surgery, Kato Clinic, Okazaki, Japan

Conflict of interest: None

[Objectives] To evaluate the clinical efficacy of add-on Igaratimod (IGU) in patients with rheumatoid arthritis despite of MTX treatment. [Methods] We used IGU treating Japanese patients with active RA. The final study cohort of each 41 patients received continuous IGU treatment more than 52 weeks. We reviewed the methods about the improvement of DAS28-ESR and CDAI which was an index of disease activity of RA. [Results] The group of patients included 6 males and 35 females. The mean age was 63.0 ± 11.0 years; the mean disease duration was 8.0 ± 8.6 years; and the mean methotrexate dose was 9.8 ± 4.2mg/week. Clinical findings related to RA were as follows: tender joint count, 5.2 ± 5.6; swollen joint count, 4.4 ± 4.4; CRP, 2.0 ± 2.4 mg/dL; ESR, 42.2 ± 19.1 mm/h; DAS28 (ESR), 4.72 ± 0.99; and CDAI, 17.5 ± 9.8. The mean DAS28 changed to 4.43 ± 1.14, 3.59 ± 1.10, 3.36 ± 1.32 and 3.19 ± 1.28 at Week 4, 12, 24 and 52 ( $p=0.004$ ,  $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ ). The mean CDAI changed to 13.7 ± 8.9, 8.8 ± 6.9, 8.4 ± 7.8 and 7.6 ± 7.2 at Week 4, 12, 24 and 52 ( $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ ). [Conclusion] This study suggested that the new combination therapy of add-on IGU with MTX was effective in patients with active RA with inadequate response to MTX.

### W16-5

#### Very early therapeutic intervention with MTX prevents the development of RA in patients with early-onset undifferentiated arthritis showing high ACPA titers

Eriko Tanaka<sup>1</sup>, Takashi Shimizu<sup>1</sup>, Takuro Nii<sup>1</sup>, Akiko Yura<sup>1</sup>, Satoru Teshigawara<sup>1</sup>, Maiko Yoshimura<sup>1</sup>, Yoshinori Harada<sup>1</sup>, Hideki Tsuboi<sup>2</sup>, Makoto Hirao<sup>2</sup>, Soichiro Tsuji<sup>1</sup>, Masato Matsushita<sup>1</sup>, Jun Hashimoto<sup>1</sup>, Shiro Ohshima<sup>3</sup>, Yukihiko Saeki<sup>3</sup>

<sup>1</sup>Department of Rheumatology and Allergology, NHO Osaka Minami Medical Center, Osaka, Japan, <sup>2</sup>Department of Orthopedics, NHO Osaka Minami Medical Center, Osaka, Japan, <sup>3</sup>Department of Clinical Research, NHO Osaka Minami Medical Center, Osaka, Japan

Conflict of interest: None

[Objectives] Previously, we showed that more than 80% of the patients with early-onset undifferentiated arthritis (EUA) showing high ACPA titers developed definite RA within a year. To examine whether very early therapeutic intervention with MTX prevents the development of RA in EUA patients showing high ACPA titers. [Methods] These prospective, controlled study included 48 patients with EUA showing high ACPA titers with no prior treatment. Based on physician's decisions, patients were treated with MTX (MTX+group,  $n=29$ ) or without MTX (MTX-group,  $n=19$ ), and the occurrence of definite RA was compared in two groups after 1 year. [Results] The percentage of patients who developed definite RA in the MTX+group (17.2%) was significantly lower than that in the MTX-group (78.9%) (log-rank test,  $p < 0.001$ ,  $n=48$ ); ad-

justed HR 0.028 [95% CI 0.003 to 0.250,  $p = 0.001$ ,  $n=39$ ]. Treatment effectiveness was not decreased by major risk factors of RA-onset such as smoking or HLA-DRB1 shared epitope (SE) (smoking, OR 0.041 [95% CI 0.007 to 0.246]  $P < 0.001$ ; SE, OR 0.022 [95% CI 0.002 to 0.204]  $p < 0.001$ ). The safety issues were comparable between the two groups. [Conclusion] Very early therapeutic intervention with MTX could safely prevent the development of RA in EUA patients showing high ACPA titers.

## W16-6

### Effectiveness and Safety of Methotrexate at the doze of 16mg/week in Patients with Rheumatoid Arthritis

Yuji Hirano, Shinya Hirabara, Masaaki Isono  
Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan

Conflict of interest: None

[Objectives] To investigate effectiveness and safety of MTX16mg/w in patients with RA. [Methods] 38 cases were used in this study. Continuation rate of MTX16mg/w, reason for stopping MTX16mg/w and disease activity before and after the administration of MTX16mg/w were investigated. [Results] Mean age was 49.7 yo. 30 female and 8 male. Mean RA duration was 6.3 y. Mean eGFR was 96.9. Continuation rates of MTX16mg/w were 86.8% at 6m, 70.1% at 1y and 41.3% at 2y. Reasons of dose reduction were liver damage in 9, bone marrow disorder in 4 and lung disorder in 3. Disease activity using DAS28, SDAI and CRP was significantly improved after MTX16mg/w administration. In case of DAS28-CRP, improvement during MTX 12mg period was significantly small compared with other periods. Association between improvement value from MTX initiation to MTX8mg/w and improvement value after MTX16mg/w initiation revealed reverse association and there was significant reverse association in CRP. [Conclusion] This study suggested that MTX16mg/w was the promising option when MTX12mg/w was not enough with respect to efficacy. Continuation rate of MTX16mg/w was relatively low and care for adverse events would be needed. Our results showed the reverse association between efficacy before MTX16mg/w and that after MTX16mg/w.

## W17-1

### Pivotal role of RANKL-expressing effector B cells in bone destruction of rheumatoid arthritis

Yuri Hirotsaki<sup>1</sup>, Hiroaki Niiri<sup>2</sup>, Shun-ichiro Ota<sup>1</sup>, Naoko Ueki<sup>1</sup>, Tsuyoshi Nakayama<sup>1</sup>, Koji Mishima<sup>1</sup>, Shoichiro Inokuchi<sup>1</sup>, Ayako Takaki<sup>1</sup>, Jin Nakagawa<sup>1</sup>, Shota Nakano<sup>1</sup>, Daisuke Oryoji<sup>1</sup>, Masahiro Ayano<sup>1</sup>, Sho Ueda<sup>1</sup>, Satomi Hisamoto<sup>1</sup>, Atsushi Tanaka<sup>1</sup>, Hiroki Mitoma<sup>1</sup>, Mitsuteru Akahoshi<sup>1</sup>, Yojiro Arinobu<sup>1</sup>, Hisakata Yamada<sup>1</sup>, Akiko Kukita<sup>3</sup>, Hiroshi Tsukamoto<sup>1</sup>, Koichi Akashi<sup>1</sup>

<sup>1</sup>Department of Medicine and Biosystemic Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, <sup>2</sup>Clinical Education Center, Kyushu University Hospital, Fukuoka, Japan, <sup>3</sup>Department of Microbiology, Faculty of Medicine, Saga University, Saga, Japan

Conflict of interest: None

[Objectives] A recent study suggested that effector B cells could directly cause bone destruction of rheumatoid arthritis (RA) via expression of RANKL, however the mechanistic insights remain largely elusive. We have sought to elucidate underlying mechanisms of RANKL expression in B cells from normal subjects and RA patients. [Methods] Levels of RANKL mRNA and protein in B cells from peripheral blood were evaluated using quantitative RT-PCR and flow cytometry, respectively. The osteoclast formation was assessed in the co-culture systems using RAW264 cells. [Results] Dual stimulation of B cells with anti-BCR and anti-CD40 significantly induced RANKL expression in B cells. Among B cell subsets, switched-memory (CD27+IgD-) B cells expressed RANKL at the highest levels and induced osteoclast formation, which is further enhanced by addition of TNF- $\alpha$ . In vitro induced RANKL-expressing B cells was characterized by expression of activated markers such as CD80 and CD86, and chemokine receptor CXCR3. Notably, sw-m B cells from RA patients expressed these surface markers at higher levels than normal subjects. [Conclusion] Our current findings suggest that upon T-depend

ent activation, sw-m B cells express RANKL and CXCR3, thereby exerting effector function in bone destruction associated with RA.

## W17-2

### Mechanism of B cell regulation by TGF- $\beta$ 3

Mariko Inoue, Tomohisa Okamura, Kaoru Morita, Toshihiko Komai, Shuzo Teruya, Yukiko Iwasaki, Keishi Fujio, Kazuhiko Yamamoto  
Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo

Conflict of interest: None

[Objectives] Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by production of autoantibodies. TGF- $\beta$  is a pleiotropic cytokine possessing immune controlling effects. Our group identified CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup> regulatory T cell (LAG3<sup>+</sup> Treg) which suppresses B cell through TGF- $\beta$ 3 and ameliorates disease activity in lupus model mice. Here we elucidate the mechanism of B cell regulation by TGF- $\beta$ 3. [Methods] B cells from C57BL/6 mice were cultured with TGF- $\beta$ 1,  $\beta$ 3. B cell proliferation and antibody production were examined. To examine the effects of TGF- $\beta$ 3 *in vivo*, Toll like receptor (TLR) 7 agonist induced lupus-like mice were treated with plasmid pCAGGS-TGF $\beta$ 3 vector. [Results] TGF- $\beta$ 3 inhibited B cell proliferation by suppressing phosphorylation of Syk under B cell receptor stimulation and inhibited antibody production under anti-CD40+IL-4 stimulation by suppressing phosphorylation of STAT6. However, under TLRs stimulations, inhibitory effects of TGF- $\beta$  were reduced and antibody productions were induced. Also, pCAGGS-TGF $\beta$ 3 vector didn't show therapeutic effect. [Conclusion] Recent work has implicated that TLRs contribute to the development of SLE. It is suggested that TLR signaling is implicated in SLE pathogenesis by affecting the sensitivity of B cells to TGF- $\beta$ 3.

## W17-3

### Amplification system of inflammation by substance P (SP)-Mas-related gene X2 (MrgX2) axis in human synovial mast cells in rheumatoid arthritis (RA)

Shintaro Mishima<sup>1,2</sup>, Yuki Okamura<sup>1,2</sup>, Kenkou Yamada<sup>1,2</sup>, Masahiko Yanagisawa<sup>1,2</sup>, Masayuki Seki<sup>1</sup>, Shu Saito<sup>1</sup>, Yasuaki Tokuhashi<sup>1</sup>, Yoshimichi Okayama<sup>2</sup>

<sup>1</sup>Orthopaedic Surgery, Nihon University School of Medicine, Tokyo, Japan, <sup>2</sup>Allergy and Immunology Group, Research Institute of Medical Science, Nihon University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] The aim of this study is to investigate 1) whether synovial mast cells (MCs) are sources of SP in RA; 2) how synovial MCs release SP; and 3) what is the responsible receptor for SP in synovial MCs. [Methods] Synovial MCs were enzymatically dispersed from synovial tissues. Synovium-derived cultured MCs were generated by culturing synovial cells. SP expression was investigated using immunofluorescence in synovial tissues. MrgX2 expression was reduced using a lentiviral shRNA silencing technique. [Results] Although the number of SP-positive (+) synovial MCs and percentage of SP<sup>+</sup> MCs in all MCs from RA patients were not significantly different from those from osteoarthritis (OA) subjects, staining pattern of SP in MCs were different. SP was localized around the cell membrane of MCs from patients with RA. This staining pattern was similar to that observed in degranulated MCs. MCs rapidly released SP following aggregation of Fc $\epsilon$ RI or addition of aggregated IgG. Tachykinin 1 mRNA level was upregulated by activation. MCs were activated with SP through MrgX2, but not through neurokinin-1R. [Conclusion] Synovial MCs release SP following aggregation of Fc $\gamma$ . Released SP activates MCs in autocrine or paracrine fashion and resulted in amplification system of inflammation

## W17-4

### Analysis of activation of platelets in rheumatoid arthritis and the effect of activated platelets on peripheral blood mononuclear cells

Shota Nakano<sup>1</sup>, Hiroki Mitoma<sup>1</sup>, Shoichiro Inokuchi<sup>1</sup>, Masahiro Ayano<sup>1</sup>, Hiroshi Tsukamoto<sup>1</sup>, Shun-ichiro Ota<sup>1</sup>, Naoko Ueki<sup>1</sup>, Satomi Hisamoto<sup>1</sup>, Sho Ueda<sup>1</sup>, Daisuke Oryoji<sup>1</sup>, Yuri Hirotsaki<sup>1</sup>, Jin Nakagawa<sup>1</sup>, Tesshin

Murakami<sup>1</sup>, Ayako Takaki<sup>1</sup>, Tsuyoshi Nakayama<sup>1</sup>, Atsushi Tanaka<sup>1</sup>, Mitsuteru Akahoshi<sup>1</sup>, Yojiro Arinobu<sup>1</sup>, Hiroaki Niuro<sup>2</sup>, Koichi Akashi<sup>1</sup>

<sup>1</sup>Department of Clinical Immunology and Rheumatology and Infectious Disease, Kyushu University Hospital, Fukuoka, Japan, <sup>2</sup>Clinical Education Center, Kyushu University Hospital, Fukuoka, Japan

Conflict of interest: None

[Objectives] It has been revealed that platelets have function of not only hemostasis but also activating the inflammatory and immune systems. The local thrombi induce inflammation and tissue damage, therefore suppressing the activation of platelets is important. On the other hand, there are few reports on the role of platelets in inflammatory diseases including rheumatoid arthritis (RA). In this study, we intend to clarify the significance of activation of platelets in RA and its role on pathogenesis of RA. [Methods] We compared activation of platelets between RA patients and healthy donors by flow cytometry. We determined inflammatory cytokines by ELISA after lipopolysaccharide (LPS) stimulation in peripheral blood mononuclear cells (PBMCs) cultured alone or PBMCs co-cultured with activated platelets. [Results] RA patients showed significantly higher expression of CD62P among CD41 positive cells than healthy donors. Secretion of IL-1b was higher after LPS stimulation in PBMCs co-cultured with activated platelets than PBMCs alone. IL-1b secretion was not observed in LPS-stimulated activated platelets alone. [Conclusion] IL-1b has recently been reported to be an onset and exacerbating factor of arthritis, hence activation of platelets may be involved in the pathogenesis of RA.

### W17-5

#### Inhibition of JAK1/3 facilitates expansion of myeloid-derived suppressor cells and ameliorates arthritis in SKG mice

Keisuke Nishimura, Jun Saegusa, Kengo Akashi, Takaichi Okano, Miwa Nishida, Soshi Takahashi, Sho Sendo, Akira Onishi, Yoshinori Kogata, Goichi Kageyama, Akio Morinobu

Department of Rheumatology and Clinical Immunology, Kobe University Graduate School of Medicine, Kobe, Japan

Conflict of interest: None

[Objectives] Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of cells that have an ability to suppress T cell responses. The aim of this study was to evaluate the effects of tofacitinib on MDSCs in a mouse model of rheumatoid arthritis. [Methods] Arthritis was induced in SKG mice by zymosan A injection. Tofacitinib was administered subcutaneously via osmotic pump. For a depletion assay, anti-Gr1 mAb was injected to mice treated with tofacitinib. We cultured BM cells with GM-CSF in the presence of selective JAK inhibitors or tofacitinib. We then analyzed the percentage of MDSCs. [Results] Significantly higher number of MDSCs in BM was observed in tofacitinib-treated group. Furthermore, administration of anti-Gr1 mAb exacerbated the arthritis of tofacitinib-treated mice. Tofacitinib facilitated the differentiation of MDSCs and inhibited the differentiation of DCs *in vitro*. Furthermore, the number of MDSCs was increased by the addition of a selective JAK1 inhibitor or a selective JAK2 inhibitor. In contrast, a selective JAK2 inhibitor did not affect the number of MDSCs. [Conclusion] Tofacitinib facilitates MDSCs differentiation through inhibiting JAK1 and/or JAK3, and ameliorates arthritis in SKG mice.

### W17-6

#### Inhibition of the each module of connective tissue growth factor is a potential therapy for rheumatoid arthritis

Tomoko Miyashita<sup>1</sup>, Shinji Morimoto<sup>2</sup>, Maki Fujishiro<sup>3</sup>, Kunishiro Hayakawa<sup>3</sup>, Keigo Ikeda<sup>2</sup>, Iwao Sekigawa<sup>2,3</sup>, Yoshinari Takasaki<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Juntendo University, School of Medicine, <sup>2</sup>Department of Internal Medicine and Rheumatology, Juntendo University Urayasu Hospital, <sup>3</sup>Institute for Environmental and Gender-Specific Medicine, Juntendo University Graduate School of Medicine

Conflict of interest: None

[Objectives] We had previously reported the importance of connec-

tive tissue growth factor (CTGF) in rheumatoid arthritis (RA). CTGF is characterized by four homologous modules. The relationships between RA and each module of CTGF are still unknown. Here, we analyzed the pathophysiological outcomes of RA resulted from the inhibition of each module of CTGF. [Methods] Stimulation and suppression experiments were conducted using the synovial cells (MH7A) from RA patient. The angiogenesis was examined by a tube formation assay using human umbilical vein endothelial cells, whereas tartrate resistant acid phosphatase staining was used to analysis the osteoclastogenesis. [Results] Tumor necrosis factor-alpha induced aberrant CTGF production in synovial fibroblast. On the other hand, the combination of recombinant Human CTGF with M-colony stimulating factor and the receptor activator of NF-kappa B ligand was found to promote the morphological changes and differentiation of CD14+ monocyte to osteoclast. Additional analysis through the tube formation assays has indicated that CTGF induced angiogenesis. These effects were neutralized by each CTGF module monoclonal antibody. [Conclusion] Not only CTGF but also each specific module of CTGF may become a new treatment of RA.

### W18-1

#### New low molecular compounds that can target transformed synovial fibroblasts in rheumatoid arthritis by screen a panel of multiple inhibitors

Tomoko Sugiura<sup>1,2</sup>, Yohko Murakawa<sup>3</sup>, Makoto Kawakami<sup>4</sup>, Masahiro Kondo<sup>3</sup>

<sup>1</sup>Institute of Biochemistry, Shimane University Faculty of Medicine, <sup>2</sup>Sugiura Clinic, <sup>3</sup>Institute of Rheumatology, Shimane University Faculty of Medicine, <sup>4</sup>Tamatukuri Hospital

Conflict of interest: None

[Objectives] To find new low molecular compounds that can target transformed synovial fibroblasts in rheumatoid arthritis (RA). We focused on invasive phenotypes of RA synovial fibroblasts because they invade cartilage, causing joint damage. [Methods] A panel of multiple inhibitors (n = 330) was screened using the xCELLigence Real-Time Cell Analysis to search for drugs that inhibit the invasion/migration of RA synovial fibroblasts. [Results] Several candidate inhibitors were identified, including inhibitors for the platelet-derived growth factor receptor (PDGFR), Akt, phosphoinositide 3-kinase (PI3K), and glycogen kinase synthetase-3 $\beta$ . Interestingly, all of them formed a unique signaling cascade from the cell surface receptor (PDGFR) to the intracellular signaling molecules, Akt/PI3K/GSK-3 $\beta$ , as confirmed through immunoblotting by using anti-phospho-Akt/PI3K/GSK-3 $\beta$  antibodies. These drugs also inhibited synovial fibroblast migration and proliferation, and some of the inhibitors suppressed PDGF-induced metalloproteinase-3 production. These inhibitors would suppress invasion of synovial fibroblasts that predominantly block cell migration and inhibit either a PDGFR step or downstream pathway. [Conclusion] Blocking of Akt/PI3K/GSK-3 $\beta$  has a therapeutic value for RA treatment.

### W18-2

#### IL-6 signaling modulates expression of clock genes via transcription regulator ROR $\alpha$ in rheumatoid synovial cells

Kenta Kaneshiro<sup>1</sup>, Teppei Hashimoto<sup>2,3</sup>, Kohsuke Yoshida<sup>1</sup>, Yoshiko Kawasaki<sup>3</sup>, Koji Tateishi<sup>4</sup>, Natsuko Nakagawa<sup>4</sup>, Nao Shibamura<sup>5</sup>, Hironori Tateishi<sup>3,5</sup>, Akira Hashiramoto<sup>1</sup>

<sup>1</sup>Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, <sup>2</sup>Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, <sup>3</sup>Department of Rheumatology, Kobe Kaisei Hospital, Kobe, Japan, <sup>4</sup>Department of Orthopaedic Surgery, Konan-Kakogawa Hospital, Kakagawa, Japan, <sup>5</sup>Department of Orthopaedic Surgery, Kobe Kaisei Hospital, Kobe, Japan

Conflict of interest: None

[Objectives] The circadian rhythm of mammals is controlled by clock genes including *Per2*, *Bmal1*, *Cry* and *Clock*. A recent study reported the expression of transcription regulator Retinoid-Related Orphan Receptor alpha (ROR $\alpha$ ) affected on apoptosis-induction of cells. Since we previously demonstrated IL-6 signaling of rheumatoid synovial cells contributed to acquire the resistance for apoptosis via inhibition of *Per2* ex-

pression, in this study, we investigated the regulation between *RORα* and *Per2* genes expression. [Methods] Total RNA was extracted from primary cultured human synovial cells under the stimulation with IL-6/IL-6R (100 ng/ml). Anti human IL-6R monoclonal antibody (anti hIL-6 mAb) was tested for inhibition of IL-6 signaling. Quantitative PCR was performed for analyzing *Per2*, *Bmall* and *RORα* genes expression. [Results] Co-stimulation of IL-6/IL-6R inhibited expression of *Per2*, *Bmall* and *RORα*, which was cancelled by anti hIL-6 mAb. [Conclusion] IL-6 signaling modulates expression of *RORα* to induce inhibitions of *Bmall* and *Per2* expression. Results suggest a novel mechanism of IL-6 signaling in synovial cells to acquire the resistance for apoptosis-induction

### W18-3

#### ADAM-17 is correlated with disease activity and mediates monocyte adhesion in rheumatoid arthritis

Sho Ishii<sup>1</sup>, Takeo Isozaki<sup>1</sup>, Kuninobu Wakabayashi<sup>1</sup>, Yusuke Miwa<sup>1</sup>, Tsuyoshi Kasama<sup>1</sup>, Katsunori Inagaki<sup>2</sup>, Masanori Nakamura<sup>2,3</sup>, Yoichi Toyoshima<sup>2</sup>, Koei Oh<sup>3</sup>

<sup>1</sup>Division of Rheumatology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan, <sup>2</sup>Department of Orthopedics, Showa University School of Medicine, Tokyo, Japan, <sup>3</sup>Department of Orthopedics, Showa University Northern Yokohama Hospital, Yokohama, Japan

Conflict of interest: None

**Objective:** A disintegrin and metalloproteinase 17 (ADAM-17), also known as tumor necrosis factor- $\alpha$  converting enzyme (TACE), have been reported to be involved in a number of inflammatory conditions. We examined the expression of ADAM-17 in rheumatoid arthritis (RA) biological fluids and the role it plays in monocyte adhesion. **Methods:** ADAM-17 expression was measured by enzyme-linked immunosorbent assay and immunofluorescence. To determine the role of ADAM-17 in RA, RA synovial fibroblasts were transfected with siRNA against of ADAM-17. Fractalkine/CX3CL, and vascular endothelial cell growth factor (VEGF) were measured. Finally, THP-1 adhesion assay was performed. **Results:** The expression of ADAM-17 in RA serum and synovial fluids was significantly higher compared to normal serum and was correlated with a disease activity score of 28. ADAM-17 siRNA inhibited THP-1 adhesion to RA synovial fibroblasts. Finally, we found that blocking ADAM-17 expression in RA synovial fibroblasts resulted in decreased fractalkine/CX-3CL1 and VEGF production. **Conclusion:** This study indicates that ADAM-17 plays a role in production of inflammatory cytokines and monocyte adhesion in RA. Targeting ADAM-17 may provide a method by which to decrease inflammation and potentially treat other inflammatory diseases.

### W18-4

#### Tankyrase regulates osteoclast differentiation

Shunichi Fujita, Tomoyuki Mukai, Yoshitaka Morita

Department of Rheumatology, Kawasaki Medical School, Kurashiki, Japan

Conflict of interest: None

[Objectives] Tankyrase 1/2 are poly (ADP ribose) polymerases and degrade several proteins including SH3BP2 and beta-catenin. SH3BP2 plays an essential role in osteoclastogenesis, however the role of Tankyrase in osteoclastogenesis is not clarified. The aim of this study is to investigate the role of Tankyrase in osteoclast differentiation. [Methods] Murine pre-osteoclastic RAW264.7 cells were treated with either RANKL (50 ng/ml) or TNF (25 ng/ml) in the presence of Tankyrase inhibitors (IWR-1 and XAV-939) or Wnt inhibitors (IWP-2 and C59). Osteoclast differentiation was determined by TRAP-positive multinucleated cells (TRAP+ MNCs). SH3BP2 protein levels were determined by Western blotting. [Results] IWR-1 and XAV-939 enhanced both RANKL- and TNF-induced osteoclast differentiation in a concentration-dependent manner. IWR-1 (2  $\mu$ M) and XAV-989 (5  $\mu$ M) increased the area of TRAP+ MNCs by 5-10 fold. SH3BP2 expression levels were increased in IWR-1- and XAV-939-treated cells. Meanwhile, Wnt inhibitors (IWP-2 and C59) did not significantly affect osteoclast formation. [Conclusion] These data suggest that Tankyrase inhibitors enhance osteoclast differentiation via increased SH3BP2 expression. Tankyrase could be a novel

regulator of osteoclastogenesis.

### W18-5

#### Hypoxia-inducible factor-3 $\alpha$ gene single nucleotide polymorphisms found in the patient with connective tissue diseases-related pulmonary arterial hypertension

Katsutoshi Mizumoto<sup>1</sup>, Yuichi Makino<sup>1</sup>, Ryota Yoshimoto<sup>1</sup>, Kouhei Eguchi<sup>1</sup>, Daisuke Fujishiro<sup>1</sup>, Satoru Kodama<sup>1</sup>, Atsushi Kobayashi<sup>1</sup>, Keiji Komura<sup>1</sup>, Kensaku Okamoto<sup>1</sup>, Kyohei Takatori<sup>1</sup>, Sayaka Takatori<sup>1</sup>, Yasushi Kawaguchi<sup>2</sup>, Masakazu Haneda<sup>1</sup>

<sup>1</sup>Division of Metabolism and Biosystemic Science, Department of Medicine, Asahikawa Medical University, Asahikawa, Japan, <sup>2</sup>Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

Pulmonary arterial hypertension (PAH) is a complication contributing to morbidity and mortality in the patients with connective tissue diseases (CTDs). Upregulation of endothelin-1 (ET-1) in pulmonary artery is suggested as a pathogenesis of PAH. Mechanism of such dysregulation of ET-1 expression, however, is still elusive. Hypoxia-inducible factor (HIF) is a heterodimer composed of HIF- $\alpha$  and HIF- $\beta$  subunits, participating in transcriptional regulation of genes involved in response to hypoxic conditions. We have demonstrated ablation of HIF-3 $\alpha$  gene in mice resulted in human PAH-like cardio-pulmonary phenotype with upregulation of ET-1. According to this observation, we analyzed the occurrence of HIF-3 $\alpha$  gene polymorphism in the patients with systemic sclerosis (SSc) complicated with PAH, and demonstrated certain types of single nucleotide polymorphism (SNP) in HIF-3 $\alpha$  gene are found with higher incidence than in SSc without PAH or normal populations. When HIF-3 $\alpha$  gene carrying those SNPs were overexpressed in cultured cells, HIF-3 $\alpha$  complex bound to ET-1 promoter and induced ET-1 mRNA expression stronger than wild type HIF-3 $\alpha$  complex did. Taken together, PAH-associated SNPs in HIF-3 $\alpha$  gene might contribute to the derangement of ET-1 gene regulation in patients with CTD-PAH.

### W18-6

#### Down-regulation of hypoxia-inducible factor-1 alpha and vascular endothelial growth factor by HEXIM1 attenuates myocardial angiogenesis in a mouse model of pulmonary hypertension

Noritada Yoshikawa<sup>1</sup>, Osamu Hosono<sup>1</sup>, Hiroshi Kobayashi<sup>1</sup>, Aya Oda<sup>1</sup>, Erika Matsubara<sup>1</sup>, Ryo Matsumiya<sup>1</sup>, Masaaki Uehara<sup>1</sup>, Hiroto Tanaka<sup>1,2</sup>

<sup>1</sup>Department of Rheumatology and Allergy, IMSUT Hospital, Institute of Medical Science, the University of Tokyo, <sup>2</sup>Division of Rheumatology, Center for Antibody and Vaccine, IMSUT Hospital, Institute of Medical Science, the University of Tokyo

Conflict of interest: None

[Objectives] Pulmonary hypertension (PH) associated with rheumatic diseases causes fatal right ventricular hypertrophy (RVH). Previously, we revealed that cardiomyocyte-specific HEXIM1 transgenic mice (HEX-CTg) ameliorate RVH in hypoxia-induced PH model, however, precise mechanism of HEXIM1 action remains unknown. Here we analyzed the effect of HEXIM1 on the expression of proangiogenic factors HIF-1 $\alpha$  and VEGF and on myocardial angiogenesis of RV in PH. [Methods] We infected HEXIM1-expressing adenoviruses into HeLa cells or neonatal rat cardiomyocytes (NRCMs), cultured the cells under normoxic or hypoxic condition, and examined effects of HEXIM1 on expression of HIF-1 $\alpha$  protein and its target genes. We also examined effects of HEXCTg on hypoxia-induced PH model. [Results] In both HeLa cells and NRCMs, HEXIM1 inhibited hypoxia-induced HIF-1 $\alpha$  protein expression and mRNA expression of VEGF, LDH, and GAPDH. HEXCTg attenuated hypoxia-induced RVH and myocardial angiogenesis in RV wall. [Conclusion] We conclude that HEXIM1 could prevent RVH, at least in part, via suppression of myocardial angiogenesis through down-regulation of HIF-1 $\alpha$  and VEGF in the myocardium under hypoxic condition. HEXIM1 might act as a novel therapeutic bullet in PH associated with rheumatic diseases.

## W19-1

### Ultrasound-detected residual crystal deposition in the first metatarsophalangeal joints: the association with serum uric acid level and clinical characteristics in patients with gout

Yohei Seto<sup>1,2</sup>, Atsuo Taniguchi<sup>1</sup>, Naomi Ichikawa<sup>1</sup>, Hisashi Yamanaka<sup>1</sup>

<sup>1</sup>Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, <sup>2</sup>Department of Rheumatology, Tokyo Women's Medical University Yachiyo Medical Center, Yachiyo, Japan

Conflict of interest: None

[Objectives] To determine the association between residual crystal deposition in the first metatarsophalangeal (MTP1) joints detected by ultrasonography (US) and clinical characteristics including serum uric acid (sUA) level in patients with gout. [Methods] US was performed in patients who visited our clinic for regular visits. Each patient was assessed for residual crystal deposition in bilateral MTP1 joints. Association was analyzed between US findings and clinical backgrounds including average serum uric acid level in the last 5 years. [Results] Total of 77 patients (154 MTP1 joints) were evaluated. Crystal deposition of any types was found in 51 patients. Although we did not find any association between overall findings of residual crystal deposition and clinical characteristics, there were correlations between double contour sign (DCS) and average sUA level in the last 5 years, and between tophus-like lesion and duration of follow-up, respectively. [Conclusion] Significance of US-detected crystal deposition may vary. DCS could disappear by tight control of sUA level.

## W19-2

### Efficacy of <sup>18</sup>F-Fluoro-Dexoxyglucose Positron Emission Tomography/Computed Tomography in Diagnosis of Polymyalgia-Like Illness (Second Report)

Hideyuki Horikoshi<sup>1</sup>, Takashi Nakanishi<sup>1</sup>, Rika Yonezawa<sup>1</sup>, Satsuki Aochi<sup>1</sup>, Reiko Takahashi<sup>1</sup>, Kanami Tongu<sup>2</sup>, Junko Nishioka<sup>2</sup>, Yuichi Nishioka<sup>2</sup>, Fumihiko Kimura<sup>1</sup>, Kenji Itoh<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, National Defense Medical College, Saitama, Japan, <sup>2</sup>Nishioka Clinic for Rheumatic Diseases and Allergic Diseases

Conflict of interest: None

[Objectives] Polymyalgia rheumatica (PMR) is a clinical syndrome that affects the elderly and is characterized by proximal muscle pain. However, various diseases such as malignant tumors and infections show similar clinical presentation. Therefore, they are considered as Polymyalgia-like illness, and differential diagnosis is needed. We report the findings of <sup>18</sup>F-fluoro-dexoxyglucose positron emission tomography/computed tomography (FDG PET/CT) in diagnosing Polymyalgia-like illness. We increased the number of cases and conducted further analysis. [Methods] In total, 25 cases of polymyalgia-like illness (17 PMR, 3 paraneoplastic syndrome, 2 infection, 1 vasculitis, 2 others) were analyzed by FDG PET/CT. [Results] All patients met the PMR diagnostic criteria and showed similar clinical presentation. FDG PET/CT revealed that all PMR cases showed multiple high FDG uptakes in PMR-specific sites, including the shoulder, hip, spinous processes, ischial tuberosities, and greater trochanters, while non-PMR cases showed weak FDG uptake in a single or a few PMR-specific sites. [Conclusion] FDG PET/CT is useful in the differential diagnosis of Polymyalgia-like illness.

## W19-3

### Extensive MRI Osteitis is associated with Rapid Radiographic Progression in early but not advanced Rheumatoid Arthritis

Kou Katayama<sup>1</sup>, Satomi Abe<sup>2</sup>, Tamotsu Kamishima<sup>3</sup>

<sup>1</sup>Katayama Orthopedic Rheumatology Clinic, <sup>2</sup>Department of Orthopedic Surgery, Asahikawa Medical University, <sup>3</sup>Faculty of Health Science, Hokkaido University

Conflict of interest: None

[Objectives] (1) To investigate the relationship between MRI osteitis and US finding (2) To find association between MRI osteitis, US finding and joint damage in conventional radiography (CR) (3) To clarify MRI

osteitis is associated with RRP in early or advanced RA [Methods] Gd-enhanced MRI (0.3T) of affected hand were evaluated by the RAMRIS. Joint damages in both hands and feet by the CR were also evaluated by the mTSS. Gray scale (GS) and power Doppler (PD) images of articular synovitis in metacarpophalangeal (MCP) and wrist joints were evaluated by the method proposed by EULAR. Twenty-nine RA patients with extensive MRI osteitis (RAMRIS osteitis score  $\geq 10$ ) were further analyzed. [Results] (1) Weak trend was observed between MRI synovitis score and US PD score ( $r=0.36$ ,  $p=0.06$ ). (2)  $\Delta$ mTSS/year as index of RJD was only correlated with MRI osteitis ( $r=0.45$ ,  $p=0.014$ ). (3)  $\Delta$ mTSS/year in advanced RA was significantly less compared with that in early RA regardless of high osteitis score ( $p<0.0001$ ). Percentage of RRP in early RA (14/14; 100%) was higher than that in advanced RA (2/15; 13.3%). [Conclusion] Extensive MRI osteitis reflect RJD compared with MRI synovitis, US GS and PD's inflammatory findings. Extensive MRI osteitis is associated with RRP in early RA, but not in advanced RA.

## W19-4

### Prediction of synovitis-positive joints of the hand in rheumatoid arthritis using contrast-enhanced magnetic resonance imaging with maximum intensity projection

Takanori Akai<sup>1,2</sup>, Ryo Oda<sup>1</sup>, Daigo Taniguchi<sup>1</sup>, Maki Asada<sup>1</sup>, Shogo Toyama<sup>1</sup>, Daisaku Tokunaga<sup>1</sup>, Hiroyoshi Fujiwara<sup>1</sup>, Takahiro Seno<sup>3,4</sup>, Yutaka Kawahito<sup>3</sup>, Toshikazu Kubo<sup>1,4</sup>

<sup>1</sup>Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>2</sup>Department of Orthopaedics, Otsu Municipal Hospital, Shiga, Japan, <sup>3</sup>Department of Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>4</sup>Department of Rheumatic Diseases and Joint Function, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: None

**Objectives** Contrast-enhanced magnetic resonance imaging (MRI) with maximum intensity projection (MIP) is useful for evaluating joint synovitis in rheumatoid arthritis (RA). The purpose of this study is to examine the prognosis of synovitis-positive joints on MIP imaging. **Methods** Twenty RA patients (wrist, 40 joints; metacarpophalangeal (MCP) joint, 200 joints) were included in this study. All patients were examined using MIP imaging and plain X-rays of bilateral hands, and plain X-rays were re-evaluated more than 1 year later. Evaluation of synovitis on MIP imaging was classified into three stages: strongly positive; weakly positive; and negative. Evaluation of plain X-rays was performed using Sharp score. Each joint was classified into three groups by MIP score, and whether Sharp score progressed was examined. **Results** Joint space narrowing score progressed significantly only in the MIP strongly positive group of the wrist joint. In MCP joints, joint narrowing score progressed significantly in all groups. **Conclusion** In this study, wrist joint space narrowing score was related to the degree of synovitis. However, joint space narrowing progressed regardless of synovitis in the MCP joint. Joint space narrowing requires monitoring, regardless of the degree of synovitis.

## W19-5

### The development of new measurement method in radiographic image The measurement of joint space distance by using super resolution image processing and curve fitting method

Koji Funahashi, Toshihisa Kojima, Nobunori Takahashi, Shuji Asai, Yutaka Yoshioka, Toki Takemoto, Kenya Terabe, Nobuyuki Asai, Naoki Ishiguro

Nagoya University Hospital

Conflict of interest: None

[Objectives] Because 1 pixel equals 0.15mm in the DICOM standard, we cannot identify the detection of the change which is lower than 0.15mm. We try to solve a limit of the resolution by super-resolution image processing and validate new measurement procedure of joint space distance (JSD). [Methods] We prepared the super-resolution image of metacarpocarpal (MCP) joint with radiographs. After that we drew curved line on the joint surface of MCP joint with app by several times of

manual operation. We measured JSD by two methods, integration of joint space area and using normal line. We measured JSD of bilateral 2-5MCP joints (8 joints). We also measured the JSD with normal resolution image and investigated interobserver reliability in two examiners. [Results] In 6 of 8 joints, the measurement with super-resolution image is significantly different from its with normal resolution image by *f* test. As for interobserver reliability, there were no significant differences in 4 of 8 joints with the integration method, in 5 of 8 joints by the normal line method. Most of the difference of measurements were less than 0.1mm. [Conclusion] The accuracy of JSD measurement was improved by using super-resolution image processing. We revealed that the potential that we can detect less than 0.1mm distance.

### W19-6

#### Cross-sectional study of related factors and the prevalence of severe upper level cervical lesions associated with rheumatoid arthritis

Hiromitsu Takaoka, Kosei Kawakami, Ryo Hiroshima, Naoko Koenuma, Takeshi Mochizuki  
Kamagaya General Hospital

Conflict of interest: None

[Objectives] To investigate the prevalence of severe spinal lesions in patients with rheumatoid arthritis (RA), and to analyze the related factors. [Methods] 245 patients with RA without spine surgical history. Radiographical cervical findings were classified as atlantoaxial subluxation (AAS), vertical subluxation (VS), subaxial subluxation (SAS), and spinal canal stenosis (SCS). "Severe" extents were defined as AAS with atlanto-dental interval 10mm or more, VS with Ranawat value 10 mm or less, and SAS with translation 4mm or more at multiple levels. SCS was defined as less than 13mm in the upper cervical space available for spinal cord. Examination items, gender, age, disease duration, age of onset, RF, anti-CCP antibody, DAS-CRP, DAS-ESR, SDAI, CDAI, HAQ, General VAS, pain VAS, joint surgery history, biologics, MTX, steroids, and osteoporosis. [Results] The prevalence of severe AAS, VS, or SAS was 1.6%, 3.2%, and 4.1%. Cases of SCS was 3.7%. Significant related factors were high anti-CCP antibody, high HAQ, high General VAS, joint surgery history, steroid use, and osteoporosis. [Conclusion] The high HAQ patients who does not have the joint disorder should consider to suspect spinal lesions positively.

### W20-1

#### The comparison of cytokines, chemokines and vascular growth factor profile during biologics treatment

Naoki Iwamoto<sup>1</sup>, Kosuke Fukuda<sup>2</sup>, Toshiyuki Aramaki<sup>2</sup>, Kunihiro Ichinose<sup>1</sup>, Kaoru Terada<sup>2</sup>, Yukitaka Ueki<sup>2</sup>, Atsushi Kawakami<sup>1</sup>  
<sup>1</sup>Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, <sup>2</sup>Sasebo Chuo Hospital

Conflict of interest: None

Objective) To examine the serum level of cytokines, chemokines, vascular growth factors during the biologics treatment. Method) The patients with rheumatoid arthritis (RA) treated with tocilizumab (TCZ) (n=28), etanercept (ETA) (n=36), infliximab (IFX) (n=23) were enrolled. Clinical disease activity as disease activity score (DAS) 28-ESR and serum levels of GM-CSF, IL-17, IL-6, IL-1b, IL-1ra, IL-1a, TNF- $\alpha$ , MCP-1 and VEGF using multiplex suspension array were examined at baseline and after introduction of biologics treatment. Result) The serum levels of VEGF were significantly decreased during ETA and TCZ treatment. ETA treatment decreased serum levels of IL-1ra, GM-CSF and increased serum levels of TNF- $\alpha$ . In good responder according to EULAR response criteria, TCZ decreased serum levels of TNF- $\alpha$ . Furthermore the low baseline IL-6 levels significantly correlated the good response of ETA treatment. Conclusion) Both TNF inhibitor and IL-6 inhibitor decreased serum levels of VEGF, suggesting VEGF might become novel biomarker of RA. The baseline levels of serum IL-6 have potential to become predictor of clinical course of ETA treatment.

### W20-2

#### Identification of a novel NF- $\kappa$ B kinase, NPK1 that regulate chronic inflammation in a murine model of arthritis

Toru Atsumi, Hideki Ogura, Daisuke Kamimura, Masaaki Murakami  
Molecular Neuroimmunology, Institute of Genetic Medicine, Hokkaido University

Conflict of interest: None

[Objectives] The pathogenesis of autoimmune diseases including RA is closely linked with chronic inflammation. However, molecular mechanisms to induce chronic inflammation remain elusive. We have discovered cellular machinery (termed the inflammation amplifier) that induces an excessive production of many chemokines and IL-6 in non-immune cells, which leads to chronic inflammation in mice. We performed genome-wide functional screenings of genes that regulate the inflammation amplifier. Here we report that one of the genes acts as a novel NF- $\kappa$ B kinase that control inflammation. [Methods] RNA interference was used to knock down the candidate genes in mouse and human non-immune cell lines to assess the production of inflammatory mediators. [Results] Molecular biological and biochemical approaches were employed to demonstrate that the gene product has a kinase activity on NF- $\kappa$ B p65. We termed this kinase as NPK1, NF $\kappa$ B-phosphopoylate kinase 1. For in vivo assay, we have developed an inflammation amplifier-dependent RA model in which cytokines are injected into the joints of F759 mice lacking negative regulation of the IL-6 signal. Knock down of NPK1 gene significantly suppressed the F759 arthritis. [Conclusion] We identified a new NF- $\kappa$ B kinase, NPK1 that can be targeted for treatment of RA

### W20-3

#### Correlation between serum TSLP and ACPA in RA patients

Kensuke Koyama, Hirota Haro  
Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Yamanashi, Japan

Conflict of interest: None

[Objectives] Recent findings suggest that thymic stromal lymphopoeitin (TSLP) plays an important role in the pathogenesis of rheumatoid arthritis (RA). The blockade of TSLP inhibited arthritis severity in CAIA model. However, serum levels of TSLP were not investigated in RA. [Methods] Blood samples were obtained from 100 patients of RA and 60 patients of OA. we examined the potentiality of serum TSLP levels as a diagnostic marker and the relationship between serum TSLP and clinical parameter. [Results] The serum levels of TSLP in RA patients were significantly higher than those in OA patients. A statistically significant ( $P < 0.0001$ , OR: 30.4) increase in serum TSLP levels was observed in RA patients compared with OA patients with a cut-point value of 11.05pg/ml (sensitivity: 85% and specificity: 83.4%). Serum TSLP significantly correlated with anti-citrullinated protein antibodies (ACPA) ( $r = 0.38$ ,  $p = 0.011$ ). However, serum TSLP levels were not correlated with CRP ( $r = -0.004$ ,  $p = 0.972$ ), ESR ( $r = 0.031$ ,  $p = 0.774$ ), TNF- $\alpha$  ( $r = 0.083$ ,  $p = 0.447$ ) and MMP-3 ( $r = -0.082$ ,  $p = 0.982$ ). [Conclusion] These data strongly indicate that serum TSLP might be useful as a diagnostic marker in RA, which has positive correlation with ACPA. In addition, blocking TSLP may be an optional treatment for RA patients.

### W20-4

#### IL-33 induces Th2 and proinflammatory cytokine production by lineage-committed myeloid progenitors

Yojiro Arinobu<sup>1</sup>, Ayako Takaki<sup>1</sup>, Tsuyoshi Nakayama<sup>1</sup>, Shoichiro Inokuchi<sup>1</sup>, Jin Nakagawa<sup>1</sup>, Shota Nakano<sup>1</sup>, Yuri Hirosaki<sup>1</sup>, Masahiro Ayano<sup>1</sup>, Satomi Hisamoto<sup>1</sup>, Naoko Ueki<sup>1</sup>, Shun-ichiro Ota<sup>1</sup>, Atsushi Tanaka<sup>1</sup>, Hiroki Mitoma<sup>1</sup>, Mitsuteru Akahoshi<sup>1</sup>, Hiroaki Niirou<sup>2</sup>, Hiroshi Tsukamoto<sup>1</sup>, Koichi Akashi<sup>1</sup>

<sup>1</sup>Department of Clinical Immunology, Rheumatology, and Infectious Diseases, Kyushu University Hospital, Fukuoka, Japan, <sup>2</sup>Clinical Education Center, Kyushu University Hospital, Fukuoka, Japan

Conflict of interest: Yes

IL-33 was originally identified as a cytokine that induces Th2 type

inflammation. However, recent studies have demonstrated that IL-33 is also involved in the pathogenesis of autoimmune diseases such as rheumatoid arthritis (RA) and inflammatory bowel disease. Recently, it was reported that a fraction of CD34<sup>+</sup> hematopoietic progenitor cells express IL-33 receptor. However, the precise characterization of these progenitor cells still remains unclear. To identify the IL-33 receptor-expressing hematopoietic progenitors, we analyzed the expression of IL-33 receptor on mouse hematopoietic cells comprehensively. Consistent with the previous report, IL-33 receptor expression was observed on mature eosinophils, basophils and mast cells. In addition, the IL-33 receptor expression was also observed on the lineage-committed myeloid progenitors: eosinophil progenitors, basophil progenitors and mast cell progenitors. These progenitor cells produced Th2 and proinflammatory cytokines in response to IL-33. Surprisingly, the amount of cytokine production of these progenitor cells was greater than that of mature cells. These findings suggest that lineage-committed myeloid progenitors may also be involved in the pathogenesis of RA via proinflammatory cytokine production in response to IL-33.

## W20-5

### IL-33 is Associated with Pain in Patient with Rheumatoid Arthritis

Michihito Katayama, Toru Hirano, Yoshimasa Hamano, Atsushi Kumanogoh

Respiratory Medicine, Allergy and Rheumatic Disease, Graduate School of Medicine, Osaka University, Osaka, Japan

Conflict of interest: None

[Background] There are some reports on a novel pain mechanism associated with IL-33 in mice, but no reports on such mechanism in human. [Objective] To investigate whether there are relationship between serum IL-33 concentration and pain in patients with rheumatoid arthritis (RA). [Methods] We measured serum IL-33 concentration by enzyme-linked immunosorbent assay in patient with RA, systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and healthy controls (HC), and examine medical records, and analyzed the relationships between IL-33 and medical findings. [Results] Serum IL-33 of 20 patients of each diseases were measured. Number of patients who's serum IL-33 were higher than sensitivity of the assembly were 6 in RA, 0 in SLE, 2 in SSc and 0 in HC. In statically assessment, relevant were there in rheumatoid factor ( $p=0.047$ ) and Patient VAS (visual analog scale) with serum IL-33. No relevant were there in disease duration, serum anti-cyclic citrullinated peptide antibody, C-reactive protein, blood sedimentation rate, number of swelling and tender joints, and disease activity score 28 joints. [Conclusion] There may be a novel pain mechanism independent of inflammation in patients with RA.

## W20-6

### Interferon $\alpha$ causes SLE in association with significant expanding CD3<sup>+</sup>CD4<sup>+</sup>CD8<sup>-</sup> double negative T (DNT) cell which appears to be generated *via* defective T cell differentiation in thymus

Ken Tsumiyama, Yumi Miyazaki, Shunichi Shiozawa  
Department of Medicine, Rheumatic Disease Unit, Kyushu University Beppu Hospital, Beppu, Japan

Conflict of interest: None

[Objectives] We have shown that anti-ss, dsDNA antibody and renal diseases akin to human SLE were induced in IFN $\alpha$  transgenic mice (IFN $\alpha$  Tg). In these mice, activated and effector T cells were dominant in spleen. Further, CD3<sup>+</sup>CD4<sup>+</sup>CD8<sup>-</sup> double negative T (DNT) cells were expanded in spleen and induce glomerulonephritis. These DNT cells infiltrated into glomerular lesions. In this study, we examined T cell differentiation in the thymus to investigate the mechanism for the generation of DNT cell in relation to the pathogenesis of SLE. [Methods] The expression of CD4, CD8, CD44 and CD25 in thymocytes of IFN $\alpha$  Tg were examined under flow cytometry. Based on these markers, thymocytes were categorized into each subsets of differentiation stage. [Results] In the thymus of IFN $\alpha$  Tg, CD4<sup>+</sup>CD8<sup>-</sup> DN thymocyte was significantly increased, and CD4<sup>+</sup>CD8<sup>+</sup> double positive, CD4<sup>+</sup> and CD8<sup>+</sup> single positive thymocytes were decreased. It was noted that most of DN thymocytes remained at CD44<sup>+</sup>CD25<sup>-</sup> DN1 stage and did not differentiate beyond the

DN1 stage. [Conclusion] IFN $\alpha$  may generate DNT cells likely thru the defect in T cell differentiation in the thymus, and these DNT cells appear to be important for the development of SLE.

## W21-1

### Clinical significance of cytokine profile in adult Still's disease

Masaki Shimizu<sup>1</sup>, Natsumi Inoue<sup>1</sup>, Shinichiro Tsunoda<sup>2</sup>, Mitsuhiro Kawano<sup>3</sup>, Masami Matsumura<sup>4</sup>, Hajime Sano<sup>2</sup>

<sup>1</sup>Department of Pediatrics, School of Medicine, Institute of Medical, Pharmaceutical, and Health Sciences, Kanazawa University, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, <sup>3</sup>Division of Rheumatology, Department of Internal Medicine, School of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, <sup>4</sup>Division of General Medicine, Center for Community Medicine, Jichi Medical University School of Medicine

Conflict of interest: None

[Objectives] To investigate the clinical significance of serum cytokine profile in adult still's disease (AOSD) and systemic juvenile idiopathic arthritis (s-JIA), we analyzed serum levels of cytokines in patients with both diseases and compared them with the clinical features. [Methods] 34 patients with AOSD, 77 patients with s-JIA were analyzed. Serum levels of IL-18, IL-6, neopterin, sTNFR1 and IL-1 were quantified by ELISA. Results were compared with clinical features of AOSD. [Results] Cytokine profile of both diseases was almost similar. It was characteristic that serum IL-18 levels were extremely high in active phase and remained elevated even in inactive phase. Two distinct subsets based on their serum IL-6 and IL-18 levels were identified in AOSD as well as s-JIA. The subset with IL-18/6<5000 had a significantly severe arthritis, whereas the subset with IL-18/6>5000 was more likely to develop MAS. [Conclusion] AOSD and s-JIA are the same spectrum, which is based on the significant production of IL-18. Two subsets of patients with AOSD can be identified on the basis of their serum IL-6 and IL-18 levels. These two subsets appear to be characterized by certain distinct clinical features. Monitoring the cytokine profile with IL-18/IL-6 might be useful to predict disease course.

## W21-2

### Clinical significance of serum interleukin-18 level in the differential diagnosis of adult onset Still's disease and lymphoma associated hemophagocytic syndrome

Toshihiko Shiga<sup>1</sup>, Tetsu Itami<sup>1</sup>, Kenji Sakai<sup>1</sup>, Asuka Inoue<sup>1</sup>, Chiemi Tasaki<sup>1</sup>, Shinkai Ri<sup>1</sup>, Taeko Yumoto<sup>2</sup>, Kayo Asato<sup>1</sup>, Shoichi Hino<sup>1</sup>, Tomohiro Yano<sup>1</sup>, Kazuya Kishimoto<sup>1</sup>, Yasuaki Nagare<sup>1</sup>, Hideki Shimazu<sup>1</sup>, Yuji Nozaki<sup>1</sup>, Koji Kinoshita<sup>2</sup>, Masanori Funauchi<sup>1</sup>, Itaru Matsumura<sup>1</sup>

<sup>1</sup>Department of Hematology and Rheumatology, Kinki University School of Medicine, Osaka, Japan, <sup>2</sup>Department of Rheumatology, Sakai Hospital, Kinki University School of Medicine, Osaka, Japan

Conflict of interest: None

[Purpose] Adult-onset Still's disease (AOSD) is a systematic inflammatory disease that is associated with activation of macrophage. It has been suggested that IL-18 is associated with the pathogenesis of AOSD. AOSD shares several clinical and laboratory variables with malignant lymphoma, especially lymphoma associated hemophagocytic syndrome (LAHS). So, It is difficult to differentiate these diseases. We evaluate the clinical significance of serum IL-18 level to differentiate AOSD and LAHS. [Methods] 16 patients with AOSD and 6 patients with LAHS, who were admitted to our hospital between November 2011 and October 2014, were enrolled. AOSD patients were diagnosed according to Yamaguchi criteria. Serum concentration of CRP, LDH, GOT, GPT, ferritin, sIL-2R, IL-6 and IL-18 was determined in both AOSD and LAHS. [Results] The serum IL-18 level in AOSD patients was significantly higher than that in LAHS patients ( $p=0.0127$ ), and that of sIL-2R was lower ( $p<0.0275$ ). Between AOSD and LAHS, serum concentrations of CRP, LDH, GOT, GPT, ferritin, and IL-6 were not significantly different. The level of IL-18 in AOSD patients positively correlated with serum ferritin levels ( $r^2=0.72$ ,  $p<0.001$ ). [Conclusion] We argue that IL-18 can be a biomarker for differential diagnosis between AOSD and LAHS.



### W21-3

#### Use of serum ferritin and heme oxygenase 1 for the diagnosis of adult-onset Still's disease: preliminary report of multicenter study

Yohei Kirino<sup>1</sup>, Yasushi Kawaguchi<sup>2</sup>, Yoshifumi Tada<sup>3</sup>, Masahiro Iwamoto<sup>4</sup>, Toshiyuki Ota<sup>5</sup>, Kohei Nagasawa<sup>6</sup>, Hiroshi Tsukamoto<sup>7</sup>, Syuji Takei<sup>8</sup>, Takahiko Horiuchi<sup>9</sup>, Hidehiro Yamada<sup>10</sup>, Hiroki Takahashi<sup>11</sup>, Atsuhisa Ueda<sup>1</sup>, Akihito Ohta<sup>12</sup>, Yoshiaki Ishigatsubo<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, <sup>2</sup>Institute of Rheumatology, Tokyo Women's Medical University, <sup>3</sup>Division of Rheumatology, Department of Internal Medicine, Saga University, <sup>4</sup>Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Jichi Medical University, <sup>5</sup>Iizuka Hospital, Department of Rheumatology, <sup>6</sup>Sawara Hospital, Rheumatic Disease Center, <sup>7</sup>Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, <sup>8</sup>Kagoshima University, School of Health Sciences, Faculty of Medicine, <sup>9</sup>Department of Internal Medicine, Kyushu University Bepu Hospital, <sup>10</sup>Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna University School of Medicine, <sup>11</sup>Department of Gastroenterology, Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine, <sup>12</sup>Department of Adult and Gerontological Nursing, Saga University School of Medicine

Conflict of interest: None

[Objectives] Yamaguchi's criteria for classification of adult-onset Still's disease (AOSD) has been widely applied in clinic. However, hyperferritinemia, which is a hallmark of AOSD, is not included in the criteria. Moreover, the criteria requires differential diagnosis of malignancy, infection, etc., which has been challenging. To ask whether inclusion of serum ferritin and heme oxygenase (HO)-1 is beneficial for the diagnosis of AOSD, we carried out a multicenter retrospective study. [Methods] Under the High Cytokemia Study Group corroboration, we collected sera from a total of AOSD 111 cases. Those patients were further divided into active, remission, and relapse groups. Serum ferritin and HO-1 levels were measured in all of the collected samples by means of ELISA. Correlations between clinical symptoms, ferritin, and HO-1 were analyzed. [Results] Serum ferritin and HO-1 levels were significantly higher in active and relapsed AOSD cases, and were reduced by the treatment. Significant correlation between serum ferritin and HO-1 levels were observed. Some AOSD cases had high serum HO-1 levels even after serum ferritin levels were normalized. [Conclusion] We confirmed that serum ferritin and HO-1 serve as a biomarker for AOSD, and suggest their unique roles.

### W21-4

#### Prognostic factors of clinical course in adult-onset Still's disease

Naomi Tsuchida<sup>1,3</sup>, Yohei Kirino<sup>1,3</sup>, Yukihiro Toyota<sup>1,3</sup>, Yumiko Sugiyama<sup>1,3</sup>, Yosuke Kunishita<sup>1,3</sup>, Daiga Kishimoto<sup>1,3</sup>, Reikou Kamiyama<sup>1,3</sup>, Kaoru Minegishi<sup>1,3</sup>, Maasa Hama<sup>1,3</sup>, Ryusuke Yoshimi<sup>1,3</sup>, Mitsuhiro Takeno<sup>2,3</sup>, Atsuhisa Ueda<sup>1,3</sup>, Yoshiaki Ishigatsubo<sup>1,3</sup>

<sup>1</sup>Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan, <sup>2</sup>Clinical Laboratory Department, Yokohama City University Hospital, Yokohama, Japan, <sup>3</sup>Y-CURD Study Group

Conflict of interest: None

[Objectives] Clinical course of adult-onset Still's disease (AOSD) varies. Current study aims to identify the prognostic factors of clinical course in AOSD. [Methods] We retrospectively analyzed 41 patients fulfilling the Yamaguchi's criteria who have been followed up in our department between 2006 and 2013. We classified the patients into 3 groups (monocyclic, polycyclic and chronic) and compared clinical features. [Results] Of 41 patients, 12 were male, 29 were female. Mean age at onset was  $41.5 \pm 18.0$  yr. and mean follow up periods was  $6.4 \pm 5.5$  yr. Mean serum ferritin levels were  $11,075.2 \pm 2,262.9$  ng/ml. The course of the disease was monocyclic in 17, polycyclic in 17 and chronic 7. 43% of patients received steroid pulse therapy and 56% received immunosuppressant drugs. 49% of the patients showed recurrence and required additional therapy. There was no significant predictive factor identified at this point. [Conclusions] There was no remarkable relationship between clinical courses and clinical parameters in the study. Further analysis will be

required to identify prognostic factors in AOSD.

### W21-5

#### A fact-finding research report of Weber-Christian disease

Katsunori Tanaka, Nobuo Kanazawa, Takaharu Ikeda, Fukumi Furukawa, Wakayama Medical University, Wakayama, Japan

Conflict of interest: None

[Objectives] Weber-Christian disease is defined as a disease of unknown origin showing relapsing fever with painful subcutaneous nodules and histologically characterized as infiltration of various kinds of inflammatory cells within subcutaneous fat lobules and degeneration of adipocytes. As it is difficult to distinguish this disease from some similar disorders, including histiocytic phagocytic panniculitis, alpha 1-anti-trypsin deficiency, malignant lymphoma, lupus panniculitis, vasculitis syndrome, nodular erythema, subcutaneous Sweet's disease, definite diagnostic criteria for this disease have not yet been determined. Therefore, the objective of this study is to investigate the actual patients of this disease recently diagnosed in Japan. [Methods] The questionnaire asking number of patients diagnosed as Weber-Christian disease during last 5 years and their clinical characteristics was sent to the Departments of Dermatology and Rheumatology of universities and hospitals with more than 500 beds in Japan. [Results] Under summing up. [Conclusion] By the results of this national surveillance, it is expected that the definitive diagnostic criteria for Weber-Christian disease will be determined.

### W21-6

#### Probable Autoimmune Lymphoproliferative Syndrome (ALPS) with Tubulointerstitial Nephritis (TIN) with the symptoms of developed in acute appendicitis

Eiko Hasegawa, Akinari Sekine, Naoki Sawa, Koki Mise, Keiichi Sumida, Noriko Hayami, Tatsuya Suwabe, Junichi Hoshino, Masahiro Kawada, Aya Imafuku, Rikako Hiramatsu, Yoshifumi Ubara, Kenmei Takaichi

Nephrology Center of Toranomon Hospital, Tokyo, Japan

Conflict of interest: None

[Case] 37 years old woman was admitted with acute appendicitis. Pancytopenia, splenomegaly, lymphadenopathy and high  $\gamma$  globulinemia were observed. Antinuclear antibody and anti-dsDNA antibody were positive and complement components were decreased. The urine test showed proteinuria and hematuria. A renal biopsy confirmed a diagnosis of TIN with severe infiltration of plasma cells. Lymph node biopsy showed reactive lymphadenopathy. Regardless of once improving with an antimicrobial drug, appendicitis was recurred during hospitalization. She also developed subareolar abscess. Drainage and antimicrobial drug medication were performed. Diagnosis of ALPS was confirmed by an elevated number of Double negative T cells (DNT cells, CD3+TCR $\alpha\beta$ +CD4-CD8-). We found no mutations in the FAS, CASP10 and KRAS. It became the provisional diagnosis of ALPS and started corticosteroid treatment. Pancytopenia, proteinuria and hematuria had improved by steroid treatment. [Consideration] ALPS represents a failure of apoptotic mechanisms to maintain lymphocyte homeostasis. Although it generally manifests in childhood, the adulthood onset cases are also reported. This is the rare case of adult onset ALPS with TIN. It is important to take ALPS into consideration when we see lymphadenopathy, splenomegaly, high IgG and pancytopenia.

### W22-1

#### Ability of tocilizumab to inhibit recurrence and enable discontinuation of steroids in adult-onset Still's disease

Hiroyuki Yamashita, Masanori Kono, Yusuke Sugimori, Toshiaki Shimizu, Hiroaki Hatano, Yuko Takahashi, Hiroshi Kaneko, Akio Mimori, National Center for Global Health and Medicine

Conflict of interest: None

**Objective:** The present study focuses on how TCZ inhibits recurrence and enables discontinuation of steroids in AOSD. **Methods:** In 15

subjects, treatment outcomes of steroid monotherapy and therapy with TCZ were compared. **Results:** Mean CRP at onset and ferritin levels were higher during administration of TCZ. After TCZ was started, CRP decreased from  $0.88 \pm 1.14$  mg/dl to  $0.02 \pm 0.02$  mg/dl and ferritin decreased from  $3153.0 \pm 6865.0$  ng/dl to  $21.16 \pm 25.4$  ng/dl ( $P = 0.02$ ). The steroid dose was rapidly reduced after TCZ was started, and reduction to 20 mg was achieved an average of  $65.8 \pm 26.9$  (31-109) days after the start of the maximum dose. The average final steroid dose during remission maintenance after initiation of TCZ was  $1.2 \pm 1.6$  mg/day. In addition, it was possible to extend the interval of TCZ administration to an average of  $6.1 \pm 2.1$  months. Recurrence was not noted in 6 patients, and there was a total of 17 recurrent episodes. The rate of non-recurrence was higher after initiation of TCZ than during the overall period (100% vs 49.9%). **Conclusion:** TCZ aids in inducing and maintaining remission in AOSD patients with severe activity. TCZ enables discontinuation of steroid use and extension of the interval of TCZ administration during remission maintenance and also inhibits recurrence.

## W22-2

### Efficacy of Tocilizumab for severe Still's disease

Kako Kodama, Nobuhiro Sho, Sumiaki Tanaka, Mei Tani, Yu Matsueda, Eisuke Ogawa, Yoshiyuki Arinuma, Tatsuo Nagai, Shunsei Hirohata  
Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine

Conflict of interest: None

**Objective:** Many reports showed that tocilizumab (TCZ) was effective for severe Still's disease. On the other hand, some reports showed that the cases of TCZ-triggered HPS. To evaluate the efficacy of TCZ for treatment of Still's disease, we analyzed 4 patients with severe Still's disease who was treated with TCZ. **Methods:** Of the 15 patients with Still's disease who were treated in our hospital from 2008 until 2014, 4 patients were resistant to combination therapy using glucocorticoid (GC), cyclosporine (CyA) and methotrexate (MTX), then treated with TCZ. We reviewed their clinical charts and monitored serum levels of IL-6 and IL-18. **Results:** Mean serum level of ferritin and CRP was 51067 ng/ml and 13.68 mg/dl. Among 2 patients who were monitored serum levels of IL-6 and IL-18, serum level of IL-6 decreased after GC+CyA+MTX therapy (#1:  $259 \rightarrow 3.3$  pg/ml, #2:  $52.9 \rightarrow 2.8$  pg/ml), but not serum level of IL-18 (#1:  $79800 \rightarrow 51300$  pg/ml, #2:  $8500 \rightarrow 8200$  pg/ml). After TCZ therapy, their symptoms and serum levels of IL-18 improved. In the other 2 cases complicated with HPS, they can be improved with TCZ after plasma exchange. **Conclusions:** Our results demonstrate that TCZ is effective for severe Still's disease, and TCZ may have a mechanism to improving Still's disease by depending on IL-18.

## W22-3

### Two cases of adult onset Still's disease with *MEFV* exon3 polymorphisms treated with Tocilizumab which had different response to treatment

Remi Sumiyoshi<sup>1</sup>, Fumiaki Nonaka<sup>1</sup>, Toshimasa Shimizu<sup>1</sup>, Kiyoshi Migita<sup>2</sup>, Atsushi Kawakami<sup>3</sup>, Katsumi Eguchi<sup>1</sup>  
<sup>1</sup>Sasebo City General Hospital, Nagasaki, Japan, <sup>2</sup>National Hospital Nagasaki Medical Center, Clinical Research Center, Nagasaki, Japan, <sup>3</sup>Department of Immunology and Rheumatology, Unit of Translational Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan

Conflict of interest: None

**[Case1]** A 22-year old female presented with persistent fever, sore throat, hepatosplenomegaly and arthralgia. Laboratory tests showed increase in C-reactive protein (CRP) and ferritin, and was diagnosed with adult onset Still's disease (AOSD). Treatment of steroid hormone and methotrexate was started but was insufficient and then Tocilizumab (TCZ) 8mg/kg was introduced. Her condition improved after two courses. **[Case2]** A 65-year old male presented with persistent fever and polyarthralgia. Laboratory tests showed increased in CRP and ferritin, and was diagnosed with AOSD. Steroid hormone therapy proved ineffective, and TCZ 8mg/kg was introduced. Three days later, pancytopenia and hemophagocytosis in the bone marrow smear led to the diagnosis of macro-

phage activation syndrome (MAS), where treatment was started with liposteroid and cyclosporine. *MEFV* gene mutation analysis showed L110P/E148Q/E148Q/P369S/R408Q for Case1, and E148Q/P369S/R408Q for Case2. Both cases were compound heterozygote within exon2 and 3. We have previously reported that AOSD patients with *MEFV* gene mutations/polymorphisms have a tendency to be treatment resistant. These 2 cases also support the theory.

## W22-4

### A case of relapsed adult onset Still's disease during pregnancy and successful delivery under the combined treatment of steroid, intravenous immunoglobulin and tacrolimus

Megumi Ogawa, Saori Sakaue, Mineto Ota, Norio Hanata, Bunki Natsumoto, Harumi Shirai, Oh Sasaki, Hiroaki Harada, Mihoko Shibuya, Shuji Sumitomo, Hirofumi Shoda, Keishi Fujio, Kazuhiko Yamamoto  
Department of Allergy and Rheumatology, The University of Tokyo Hospital, Tokyo, Japan

Conflict of interest: None

A 31-year-old woman was admitted to our department with arthralgia, skin rash, and fever in 17th week of gestation of her 2nd pregnancy. Six years before admission, she was diagnosed as adult onset Still's disease (AOSD) 3 months after 1st delivery, and was treated with steroid pulse therapy and high dose PSL. After remission, her disease was maintained with 5mg of daily PSL. On admission, elevation of liver enzyme, ferritin and CRP, and thrombocytopenia were observed, and she was diagnosed as a relapse of AOSD. Steroid pulse therapy and 50mg of daily PSL could not control her disease activity. Then, the combined therapy of intravenous gammaglobulin (IVIG), high dose PSL (70mg/day), and tacrolimus was started. Her symptoms were relieved, and the dosage of PSL could be tapered. In 31st week of gestation, elevation of liver enzyme appeared again. AOSD relapse was suspected, and high dose steroid therapy was started. However, liver enzymes were continuously elevated. She got preterm PROM in 34th week of gestation. On the next day, she vaginally delivered a low birth weight infant (2195g) without congenital abnormalities. Liver enzymes were decreased immediately after delivery, thus we considered that HELLP syndrome might be occurred. We report this case with some literature review.

## W22-5

### Characteristics of mothers and infants in 75 cases of pregnancy with collagen disease

Yoshihito Ogihara<sup>1,2</sup>, Shohei Ogata<sup>1</sup>, Takasuke Ebato<sup>1</sup>, Yuki Bando<sup>3,1</sup>  
<sup>1</sup>Department of Pediatrics, Kitasato University, School of Medicine, <sup>2</sup>Ebina General Hospital, Department of Pediatrics, <sup>3</sup>Department of Pediatrics, Kitasato Medical Center

Conflict of interest: None

**[Objectives]** To examine the characteristics of mothers and infants in pregnancy with collagen disease **[Methods]** The subjects of this study were 75 cases (1.3%) of pregnancies with collagen disease among a total of 5,797 cases where our hospital conducted the delivery management between Jan. 2009 and June 2014. Complications, ANA in cord blood, anti-SS-A-antibody (Ab), and anti-SS-B-Ab were examined. **[Results]** A breakdown of underlying disease was 33 SLE, 13 MCTD, 11 SJS, and 18 others. The recorded complications were 14 premature rupture of membranes, 6 pregnancy-induced hypertension, 2 HELLP syndrome, and 1 deep vein thrombosis. The median GA was 38w5d (29w5d-41w5d), and 18 cases of premature infants, the birth weight was 2,770g (1,200-3,604g), and 23 cases were low birth weight infants. The cases of Ab-positive were 57 ANA, 39 anti-SS-A-Ab, and 12 anti-SS-B-Ab cases. Although complications of transient extrasystole, deceleration, and sinus tachycardia were observed, there were no cases that exhibited auriculo-ventricular blocks. Erythema erythema was observed in four cases, many appeared in the temporal region within two months, and all those were anti-SS-A and SS-B-Ab positive. **[Conclusion]** The careful observation is necessary during the period before the disappearance of maternal Ab.

## W22-6

### The importance of early diagnosis in RS3PE syndrome

Tomoki Origuchi<sup>1,2</sup>, Kazuhiko Arima<sup>3</sup>, Shin-ya Kawashiri<sup>3</sup>, Tomohiro Koga<sup>2</sup>, Mami Tamai<sup>2</sup>, Hideki Nakamura<sup>2</sup>, Toshiaki Tsukada<sup>4</sup>, Taiichiro Miyashita<sup>5</sup>, Keita Fujikawa<sup>6</sup>, Akinari Mizokami<sup>6</sup>, Nozomi Iwanaga<sup>7</sup>, Masako Furuyama<sup>8</sup>, Munetoshi Nakashima<sup>9</sup>, Toshiyuki Aramaki<sup>10</sup>, Yukitaka Ueki<sup>10</sup>, Yojiro Kawabe<sup>11</sup>, Takaaki Fukuda<sup>12</sup>, Katsumi Eguchi<sup>13</sup>

<sup>1</sup>Department of Rehabilitation Sciences, Graduate School of Medical Sciences, Nagasaki University, Nagasaki, Japan, <sup>2</sup>Department of Rheumatology and Immunology, Graduate School of Medical Sciences, Nagasaki University, Nagasaki, Japan, <sup>3</sup>Department of Public Health, Graduate School of Medical Sciences, Nagasaki University, Nagasaki, Japan, <sup>4</sup>Department of Internal Medicine, Aino Memorial Hospital, <sup>5</sup>Miyashita Rheumatology Clinic, <sup>6</sup>Department of Rheumatology, Isahaya General-Hospital, <sup>7</sup>Department of General Medicine, Nagasaki Medical Center, <sup>8</sup>Department of Rheumatology, Nagasaki Kita Hospital, <sup>9</sup>Department of Rheumatology, Nagasaki Atomic Bomb Hospital, <sup>10</sup>Department of Rheumatology, Sasebo Chuo Hospital, <sup>11</sup>Department of Rheumatology, Ureshino Medical Center, <sup>12</sup>Department of Rheumatology, Kurume University Medical Center, <sup>13</sup>Department of Internal Medicine, Sasebo Municipal General Hospital

Conflict of interest: None

[Objectives] To clarify the importance of early diagnosis in RS3PE syndrome. [Methods] The total of 39 cases, who were diagnosed as having RS3PE syndrome, were subjected to be analyzed the duration from the onset to the diagnosis retrospectively. [Results] Average age was 78.9±6.3 years old. All RS3PE syndrome patients had a good response to prednisolone. But more than half of the patients were diagnosed one month or more after the onset. These patients required more doses prednisolone and had relapses compared to the patients who were diagnosed within one month from the onset. [Conclusion] We suggested that early diagnosis of RS3PE syndrome was important and effected the clinical course.

## W23-1

### Differential dose-response effects of methotrexate in combination with adalimumab in biologic-naïve and biologic-exposed Japanese patients with rheumatoid arthritis: A retrospective cohort study of 7740 patients - the MELODY study

Takao Koike<sup>1</sup>, Masayoshi Harigai<sup>2</sup>, Naoki Ishiguro<sup>3</sup>, Shigeko Inokuma<sup>4</sup>, Syuji Takei<sup>5</sup>, Tsutomu Takeuchi<sup>6</sup>, Hisashi Yamanaka<sup>7</sup>, Yoshinari Takasaki<sup>8</sup>, Tsuneyo Mimori<sup>9</sup>, Katsutoshi Hiramatsu<sup>10</sup>, Shuichi Komatsu<sup>10</sup>, Yoshiya Tanaka<sup>11</sup>

<sup>1</sup>NTT Sapporo Medical Center, Sapporo Hokkaido, Japan, <sup>2</sup>Tokyo Medical Dental University Graduate School, Tokyo, Japan, <sup>3</sup>Nagoya University School of Medicine, Nagoya Aichi, Japan, <sup>4</sup>Japanese Red Cross Medical Center, Tokyo, Japan, <sup>5</sup>Kagoshima University School of Health Science, Kagoshima, Japan, <sup>6</sup>Keio University, Tokyo, Japan, <sup>7</sup>Tokyo Women's Medical University, Tokyo, Japan, <sup>8</sup>Juntendo University School of Medicine, Tokyo, Japan, <sup>9</sup>Graduate School of Medicine, Kyoto University, Kyoto, Japan, <sup>10</sup>AbbVie GK, Tokyo, Japan, <sup>11</sup>University of Occupational and Environmental Health, Kitakyushu Fukuoka, Japan

Conflict of interest: Yes

[Objectives] To assess the dose-response profile of methotrexate (MTX) in patients with rheumatoid arthritis (RA) in an all-case postmarketing surveillance of adalimumab (ADA). [Methods] Of 7740 patients enrolled in the survey, 3097 patients with DAS28-ESR data at baseline and week 24 were analyzed for effectiveness by MTX dose (>0-<4, 4-<6, 6-<8, 8-<10, and ≥10 mg/wk), and by prior biologic treatment (1996 biologic-naïve vs. 1101 biologic-exposed). Stepwise Cox regression was used to compare incidences of adverse drug reactions (ADRs) and infections in 5494 patients. [Results] Percentages of patients with low disease activity (LDA) by week 24 in the 5 MTX dose groups were 39.2% (38/97), 43.0% (122/284), 49.7% (288/580), 49.8% (408/819), and 50.5% (109/216) in biologic-naïve patients, and 15.5% (13/84), 20.0% (35/175), 24.9% (87/349), 24.4% (90/369), and 39.5% (49/124) in biologic-exposed patients. The incidences of ADRs and infections did not correlate with MTX dose. [Conclusion] Our findings indicate a dose-dependent effectiveness of MTX in Japanese RA patients receiving ADA for the first

time in Japan, and suggest that the optimal MTX dose with ADA varies substantially according to patient characteristics and is lower than previously thought for biologic-naïve patients.

## W23-2

### Efficacy and Safety of Golimumab at Different Doses in Patients with Rheumatoid Arthritis in Japan in Light of Results of Drug Use-Results Survey

Shigeki Momohara<sup>1</sup>, Masayoshi Kanbori<sup>2</sup>, Yoshimasa Ogawa<sup>2</sup>, Tsutomu Yajima<sup>3</sup>, Tomoyo Kawagishi<sup>2</sup>

<sup>1</sup>Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, <sup>2</sup>Japan Safety & Surveillance Division, Research & Development Division, Janssen Pharmaceutical K.K., Tokyo, Japan, <sup>3</sup>Biostatistics Department, Research & Development Division, Janssen Pharmaceutical K.K., Tokyo, Japan

Conflict of interest: Yes

[Objectives] The drug use-results survey was conducted to evaluate the safety and efficacy under the actual clinical conditions of usage (24weeks) of golimumab (GLM) in patients with rheumatoid arthritis (RA) in Japan. [Methods] The survey was conducted as an all-cases survey at contract facilities using a central registry system. [Results] The 24-week continuation of medication, safety and efficacy were evaluated in 4 groups of the initial dose of GLM (50mg mono (MO), 50mg+methotrexate (MTX), 100mg MO, 100mg+MTX). For the distribution of patients, 50mg+MTX was 72.4%, 100mg+MTX was 5.4% and 100mg MO was 10.3%. After 24 weeks, the continuation of medication in 100mg+MTX was 78.9% and 100mg MO was 70.0%. No significant differences in the incidence of adverse drug reactions were noted among the doses. The good or moderate response rate at the final assessment using EULAR improvement criteria (DAS28/ESR) was highest in the 100mg+MTX (70.2%) and 62.3% in the 100mg MO. [Conclusion] No obvious differences were found in the safety profile at different initial doses. 100mg MO was effective and had a high medication continuation as well as 100mg+MTX. So, it was thought that 100mg MO was one of the effective medical treatment options for the patients who could not use MTX.

## W23-3

### Clinical efficacy of golimumab therapy with or without combination of MTX in patients with rheumatoid arthritis

Toki Takemoto<sup>1</sup>, Toshihisa Kojima<sup>1</sup>, Nobunori Takahashi<sup>1</sup>, Koji Funahashi<sup>1</sup>, Shuji Asai<sup>1</sup>, Kenya Terabe<sup>1</sup>, Yutaka Yoshioka<sup>1</sup>, Nobuyuki Asai<sup>1</sup>, Masatoshi Hayashi<sup>2</sup>, Atsushi Kaneko<sup>3</sup>, Yuji Hirano<sup>4</sup>, Hisato Ishikawa<sup>5</sup>, Hideki Takagi<sup>6</sup>, Takayoshi Fujibayashi<sup>7</sup>, Naoki Ishiguro<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Nagoya University School of Medicine, <sup>2</sup>Department of Rheumatology, Nagano Red Cross Hospital, <sup>3</sup>Department of Orthopedic Surgery, Nagoya Medical Center, <sup>4</sup>Department of Rheumatology, Toyohashi Municipal Hospital, <sup>5</sup>Department of Orthopedic Surgery, Japanese Red Cross Nagoya Daiichi Hospital, <sup>6</sup>Department of Orthopedic Surgery, Nagoya Central Hospital, <sup>7</sup>Department of Orthopedic Surgery, Konan Kosei Hospital

Conflict of interest: Yes

[Objectives] It is well known that biologic DMARD (bDMARD) are more effective as part of combination regimens in patients with RA than monotherapy, but biologic monotherapy is common in clinical practice for intolerance of MTX or complications. The purpose of this study is to investigate clinical efficacy of golimumab (GLM) without combination of MTX in patients with RA. [Methods] 100 patients with RA from Tsurumi Biologics Communication Registry (TBCR) were enrolled in this study. 69 patients were treated with GLM and MTX (MTX group) and 31 patients were treated with GLM monotherapy (monotherapy group). The study endpoint was disease activity and survival rate at week 24. [Results] In both MTX and monotherapy group, DAS28-ESR was significantly decreased at week 4 and the efficacy of suppression of DAS28-ESR was held until week 24. In all period, DAS28-ESR was more in monotherapy group than that in MTX group. In bDMARD-naïve patients of monotherapy group, DAS28-ESR was significantly decreased at week 4 but in bDMARD-switch patients DAS28-ESR was decreased more

slowly. [Conclusion] GLM reduced disease activity of RA in both MTX and monotherapy group. In patients treated without combination of MTX, bDMARD-naïve patients attained significant improvement more quickly than switch patients.

### W23-4

#### Clinical usefulness of adalimumab based on glucocorticoid-free rheumatoid arthritis (RA) patients: Remission induction at 52 weeks in 159 patients

Toshiaki Miyamoto

Department of Internal Medicine and Rheumatology, Seirei Hamamatsu General Hospital, Shizuoka, Japan

Conflict of interest: None

**Objective** Clinical usefulness following 52 weeks of adalimumab (ADA) in Glucocorticoid-Free rheumatoid arthritis (RA) patients were investigated. **Methods** Subjects were 159 analyzable patients introduced to ADA at the author's institution from May 2009 to October 2013. Mean age was 53.5 years, mean duration of illness 6.3 years. 57 patients had a duration of illness below 2 years (<2) and 102 at least 2 years ( $\geq 2$ ), 114 were Bio Naïve (N), 45 were Switch (S), 132 received MTX  $\geq 10$  mg/week ( $\geq 10$ ) and 23 MTX <10 mg/week (<10). There was no significant difference in baseline disease activity. **Results** Overall DAS28 (CRP) remission rate showed clinical remission in 50% of patients from 4 weeks and 80% of patients from 52 weeks. Changes in DAS 28 (CRP) remission rates of 4, 8, 12, 24, 36, 52 weeks for the <2 and  $\geq 2$  were similar to those seen in the N and S groups, but differed from those in the  $\geq 10$  and < 10. Overall HAQ remission rate at 52 weeks was 80%. **Conclusion** Short-term a little glucocorticoid in the RA is recommended in JCR2014 guidelines, EULAR recommendation. However, the harmful phenomenon is a problem, and the glucocorticoid requires scrupulous attention about the use. Even if a glucocorticoid-free, this result suggested that a good treatment result was provided by MTX+ADA.

### W23-5

#### Investigation of clinical efficacy of adalimumab treatment on rheumatoid arthritis with disease-modifying antirheumatic drugs

Satoshi Ito<sup>1</sup>, Daisuke Kobayashi<sup>1,2</sup>, Satoru Kodama<sup>1,3</sup>, Tomo Oyakawa<sup>1,4</sup>, Kengo Harigane<sup>1,5</sup>, Asami Abe<sup>1</sup>, Hiroshi Otani<sup>1</sup>, Hajime Ishikawa<sup>1</sup>, Akira Murasawa<sup>1</sup>, Ichiei Narita<sup>2</sup>, Kiyoshi Nakazono<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Niigata Rheumatic Center, <sup>2</sup>Division of Clinical Nephrology and Rheumatology Niigata University Graduate School of Medical and Dental Sciences, <sup>3</sup>Division of Metabolism and Biosystemic Science, Department of Medicine, Asahikawa Medical University, <sup>4</sup>Department of Orthopedic Surgery, University of the Ryukyus, <sup>5</sup>Department of Orthopedic Surgery, Yokohama City University

Conflict of interest: Yes

[Objectives] To analyze the efficacy of adalimumab (ADA) in the presence of methotrexate (MTX) and disease-modifying antirheumatic drugs (DMARDs) from the baseline through 48 weeks. [Methods] Enrolled were 66 patients who started ADA from Jul 2008 to Oct 2013, followed for 48 weeks. Disease activity score 28 by erythrocyte sedimentation rate (DAS28-ESR) was recorded during ADA treatment. Patients were stratified by the number of DMARDs used at the initiation of ADA. [Results] Baseline demographic profile of 66 patients was 6 male and 60 female, mean age of 53.3 $\pm$ 12.8 years, mean disease duration of 53.3 $\pm$ 12.8 years, Steinbrocker stage (number of patients) were I (9), II (19), III (10), IV (28), and Steinbrocker class (number of patients) were I (10), II (47), III (9), IV (0). Mean DAS28-ESR at baseline and week 48 were 4.6 $\pm$ 1.6 and 3.0 $\pm$ 1.6 for 0 DMARD, 4.3 $\pm$ 1.2 and 2.8 $\pm$ 1.4 for 1 DMARD, 4.5 $\pm$ 1.6, and 2.4 $\pm$ 1.2 for patients with >1 DMARDs, respectively. Clinical remission was achieved in 52%, 46%, and 77%, of those receiving 0, 1, and >1 DMARDs respectively. There was clinical difference between concomitant use of 1 and >1 DMARDs (p=0.048). [Conclusion] Combination with a sufficient dose of MTX in the presence of additional DMARDs may enforce the clinical efficacy of ADA.

### W23-6

#### Biologic Triple Therapy with MTX, TNF inhibitor, and Tacrolimus for Active Rheumatoid Arthritis after TNF Inhibitor Failure

Taio Naniwa<sup>1</sup>, Mikiko Kajiura<sup>3</sup>, Shinya Tamechika<sup>2</sup>, Shinji Maeda<sup>2</sup>, Akio Niimi<sup>2</sup>

<sup>1</sup>Early Arthritis Clinic, Division of Respiratory Medicine, Allergy and Rheumatology, Nagoya City University Hospital, <sup>2</sup>Division of Respiratory Medicine, Allergy and Rheumatology, Nagoya City University Hospital, <sup>3</sup>Takeuchi Orthopedics & Internal Medicine

Conflict of interest: Yes

[Objectives] To assess the long-term efficacy of Biologic Triple Therapy with MTX, TNF inhibitor (TNFi), and Tacrolimus (TAC) in patients with RA and an inadequate response (IR) to TNFi [Methods] Consecutive patients who were treated by the lead author and started TAC for active TNFi-IR RA patients from Jan 2004 to Oct 2013 were analyzed in terms of the rates of achieving ACR/EULAR remission and biologic- and oral glucocorticoid-free remission for 6 and 12 months. [Results] A total of 15 patients could be analyzed. Five patients were treated sequentially with two TNFi. All were seropositive. At the onset of TAC, median disease duration was 2.9 yrs [IQR, 1.3-6.2], duration of therapy with TNFi was 9.2 months [6.4-12.2], and DAS28-esr was 4.6 [3.8-5.2]. MTX was used at the dose of 15 mg/week [10-16]. Glucocorticoids were used in 10 patients at the dose of 5.0 mg/day of prednisolone [3.3-5.0]. Twelve patients achieved glucocorticoid-free ACR/EULAR remission at 4.9 months [3.3-8.4] after the onset of TAC. Twelve patients discontinued TNFi treatment due to achieving remission or low disease activity. The rates of successful withdrawal from biologics for 6 and 12 months were 9/11 and 5/8. [Conclusions] Bio-Triple Therapy is a promising therapeutic strategy for TNF-IR RA patients.

### W24-1

#### Prevalence of lung abnormalities on the chest computed tomography in patients with microscopic polyangiitis (MPA) before receiving immunosuppressive treatment – a multicenter, cross-sectional study of 150 hospital-based consecutive Japanese patients

Mieko Yamagata<sup>1</sup>, Kei Ikeda<sup>1</sup>, Takashi Ito<sup>1,3</sup>, Daisuke Kashiwakuma<sup>3</sup>, Itsuo Iwamoto<sup>3</sup>, Daiki Nakagomi<sup>4,5</sup>, Takao Sugiyama<sup>4</sup>, Shunsuke Furuta<sup>1,5</sup>, David Jayne<sup>5</sup>, Hiroshi Nakajima<sup>1</sup>

<sup>1</sup>Department of Allergy and Clinical Immunology, Graduate School of Medicine, Chiba University, Chiba, Japan, <sup>2</sup>Department of Respiriology, Graduate School of Medicine, Chiba University, Chiba, Japan, <sup>3</sup>Research Center for Allergy and Clinical Immunology, Asahi General Hospital, Asahi, Chiba, Japan, <sup>4</sup>Department of Rheumatology, National Hospital Organization Shimoshizu Hospital, Yotsukaido, Chiba, Japan, <sup>5</sup>Lupus and Vasculitis Clinic, Addenbrooke's Hospital, Cambridge University Hospitals, Cambridge, UK

Conflict of interest: None

[Objectives] We aimed to determine the prevalence of lung abnormalities on the chest computed tomography (CT) in patients with microscopic polyangiitis (MPA) and assess their associations with patient/disease characteristics. [Methods] We retrospectively identified 167 hospital-based MPA patients in three centers in Japan. Of them, we collected clinical information of 150 patients whose CT images before treatment were available. Three pulmonologists determined the presence of 22 imaging components. [Results] A wide variety of lung abnormalities were identified in most of the patients (97%), interstitial lung lesions (66%), airway lesions (66%), pleural lesions (53%), and emphysematous lesions (37%). In multivariate analyses, three out of four airway lesions were associated with myeloperoxidase (MPO)-anti-neutrophil cytoplasm antibodies (ANCA). Latent class analysis identified three groups of the clustering patterns of lung abnormalities, characterized by the interstitial lung lesions accompanied by other lesions, the airway lesions, and the paucity of parenchymal or airway lesions. [Conclusions] Abnormalities in a wide range of anatomical areas can be identified. The prevalence and the clustering patterns of lung abnormalities will be useful for future studies about MPA.

## W24-2

### Predictors of diffuse alveolar hemorrhage in microscopic polyangiitis: A retrospective observational study

Takashi Kida<sup>1</sup>, Aiko Tominaga<sup>1</sup>, Risa Sagawa<sup>1</sup>, Amane Nakabayashi<sup>1</sup>, Kazuki Fujioka<sup>1</sup>, Yuji Kukida<sup>1</sup>, Hidetake Nagahara<sup>1</sup>, Wataru Fujii<sup>1</sup>, Ken Murakami<sup>1</sup>, Takahiro Seno<sup>1,2</sup>, Aihiro Yamamoto<sup>1</sup>, Masataka Kohno<sup>1</sup>, Yutaka Kawahito<sup>1</sup>

<sup>1</sup>Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>2</sup>Department of Rheumatic Diseases and Joint Function, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: None

[Objectives] To investigate predictors of diffuse alveolar hemorrhage (DAH), we evaluated the clinical characteristics of patients with microscopic polyangiitis (MPA). [Methods] We analyzed retrospectively 69 patients (the mean age of onset was 69.2 years and the mean BVAS at diagnosis was 20.1) diagnosed with MPA at two institutes (Kyoto Prefectural University of Medicine and Matsushita Memorial Hospital) from January 2006 to October 2014. [Results] 20 patients (29.0%) were complicated with DAH, and 19 of them presented DAH prior to initiation of treatment. Their survival rates decreased in the early phase. 48 patients (69.6%) presented underlying pulmonary involvements except DAH, and which were classified into two patterns based on CT imaging: 21 cases of interstitial pneumonia (IP) and 27 cases of bronchiectasis (BE). 15 of 20 patients with DAH presented BE, and a significant association between BE and DAH was found ( $P < 0.05$ ). Rapidly progressive glomerulonephritis (RPGN) was detected in 49 patients (71.0%). 18 of them presented DAH, and a significant association between RPGN and DAH was found ( $P < 0.05$ ). In 16 cases, RPGN preceded or co-occurred with DAH. [Conclusion] In this study, DAH was frequently accompanied by BE or RPGN. These factors might be useful predictors of DAH.

## W24-3

### Prognostic factors for interstitial lung disease with microscopic polyangiitis

Takeshi Shoda, Tohru Takeuchi, Shigeki Makino, Takuya Kotani, Takaaki Ishida, Hideyuki Shiba, Youhei Fujiki, Toshiaki Hanafusa  
1st Department of Internal Medicine, Osaka Medical College, Osaka, Japan

Conflict of interest: None

[Objectives] To investigate the prognosis of pulmonary fibrosis with microscopic polyangiitis (MPA-ILD) and prognostic factors. [Methods] Of patients with MPA who were admitted to our hospital between 2001 and 2013, the subjects were MPO-ANCA-positive patients with ILD on HRCT. Using the clinical data and fibrosis score on HRCT, we examined prognostic factors. [Results] There were 42 patients with MPA-ILD, consisting of 20 males and 22 females, with a median age of 73 years. MPO-ANCA, KL-6, %FVC, and %DLco/VA values at the start of treatment were 189EU, 446U/mL, 81.3%, and 61.4%, respectively. Concerning HRCT images, 30 patients showed a UIP pattern. In 37 patients, it was combined with immunosuppressive drugs. In 8, apheresis was performed. In 37 patients, the MPO-ANCA level was maintained below the detection limit. With respect to the prognosis, 8 patients died. The 5-year survival rates after the treatment were 85.2%. Univariate analysis for lung disease-associated death included the HRCT score ( $p < 0.001$ ), WBC ( $p = 0.007$ ), and CPFE ( $p = 0.004$ ). However, on multivariate analysis of these factors, the HRCT score was significantly correlated ( $p = 0.005$ ). [Conclusion] HRCT fibrosis score at the start of treatment were considered to be prognostic factors for lung disease-associated death.

## W24-4

### Eosinophilic Granulomatosis with Polyangiitis Flare with Cytomegalovirus reactivation

Ai Yaku<sup>1</sup>, Shuko Hashimoto<sup>1</sup>, Teruhisa Azuma<sup>1</sup>, Hiroyasu Ishimaru<sup>1</sup>, Kazuhiro Hatta<sup>1</sup>, Kumi Fujita<sup>2</sup>

<sup>1</sup>Department of General Internal Medicine, Tenri Hospital, Tenri, Japan, <sup>2</sup>Department of Clinical Pathology, Tenri Hospital, Tenri, Japan

Conflict of interest: None

[Case] A 60-year-old male with asthma was admitted to our hospital with fever, asthma flare-up, abdominal pain, and bilateral lower limb numbness. Eosinophilia (WBC  $17.4 \times 10^3 \mu\text{L}$ , Eo 22%), MPO-ANCA (233 U/ml), intestinal edema, and mononeuritis multiplex were detected. He was diagnosed with eosinophilic granulomatosis with polyangiitis and treated with a steroid pulse, prednisolone 60 mg/day, and IVCY, which could not control the vasculitis. Rituximab was administered, but fever and eosinophilia lasted and paralysis occurred. Plasma exchange (PE) reduced the fever and decreased the eosinophilia levels. Two weeks after PE, he had sudden chest pain and fever, with an abnormal ECG and increased cardiac enzyme levels. Coronary angiography showed complete occlusion of #4PL and #12. We assumed this was not due to arteriosclerosis but rather vasculitis, as the lesions were peripheral from main coronaries. We concluded acute myocarditis caused by vasculitis. We looked for the trigger as vasculitis flare under maximum treatment was highly unusual. We treated CMV antigenemia, which occurred before the myocarditis. Fever, eosinophilia, and CRP elevation were resolved. [Discussion] Infection can trigger an autoimmune disease. In this case, CMV reactivation may have triggered the vasculitis.

## W24-5

### Efficacy of high-dose intravenous immunoglobulin therapy for peripheral neuropathy with eosinophilic granulomatosis with polyangiitis assessed by the nerve conduction study

Rika Yonezawa, Hideyuki Horikoshi, Takashi Nakanishi, Satsuki Aochi, Reiko Takahashi, Fumihiko Kimura, Kenji Itoh  
Division of Hematology and Rheumatology, Department of Internal Medicine, National Defense Medical College, Tokorozawa, Japan

Conflict of interest: None

[Objectives] Peripheral neuropathy is one of the intractable complications associated with eosinophilic granulomatosis with polyangiitis (EGPA). The efficacy of high-dose intravenous immunoglobulin (IVIg) in treating the neuropathy of EGPA has been recently reported. However, the therapeutic efficacy of IVIg has not been evaluated by objective and quantitative analyses. We report the efficacy of IVIg for peripheral neuropathy complicated with EGPA, confirmed with the nerve conduction study (NCS). [Methods] Four cases of peripheral neuropathy complicated with EGPA were treated with corticosteroid alone or were followed with IVIg. The therapeutic efficacy was evaluated by conventional physical examinations and NCS before and after treatments. [Results] After the induction therapy with corticosteroid, patients' clinical symptoms demonstrated partial improvement. Two out of four patients received IVIg after corticosteroid therapy. In addition to other clinical improvements, IVIg-treated cases showed more improvement in the amplitude of distal compound muscle action potentials and sensory nerve action potentials in NCS than before receiving IVIg. [Conclusion] NCS findings confirmed that IVIg was effective for intractable peripheral neuropathy complicated with EGPA.

## W24-6

### Relapse prevention effect of immunosuppressants in patients with eosinophilic granulomatosis with polyangiitis

Aiko Saku, Kenichi Suehiro, Sohei Makita, Mieko Yamagata, Shunsuke Furuta, Kei Ikeda, Koichi Hirose, Hiroshi Nakajima  
Chiba University Hospital, Department of Allergy and Clinical Immunology

Conflict of interest: None

Purpose: Although corticosteroid is effective for eosinophilic granulomatosis with polyangiitis (EGPA), patients treated with corticosteroid monotherapy often experience relapses. Immunosuppressants such as cyclophosphamide (CY) are occasionally used with corticosteroid mainly for refractory and severe cases; however, the position of immunosuppressants in the treatment of EGPA is still obscure. In this study, we assessed relapse prevention effect of CY for newly diagnosed EGPA. Methods: Subjects were 37 EGPA patients who diagnosed in Chiba University Hospital between 1996 and 2014. All patients met the diagnostic criteria

by Ministry of Health, Labour and Welfare. Patient characteristics, treatments, and relapses were assessed by retrospective chart reviews. Results: As remission induction therapy, 26 patients received corticosteroid monotherapy, while 11 patients received corticosteroid plus CY therapy (CY group). CY was followed by azathioprine in 5 patients. The median age at onset in monotherapy group vs. CY group was 59.5y vs. 59.0y ( $p=0.92$ ), MPO-ANCA positivity was 34.6% vs. 72.7% ( $p=0.03$ ) and disease free survival rates at 1 and 5 years were 87.5% vs. 100% and 58.7% vs. 100% ( $p=0.08$ ), respectively. Conclusion: Relapses tended to be less frequent in CY group than monotherapy group.

## W25-1

### Novel monoclonal anti-phosphatidylserine-prothrombin complex antibody induces thrombosis in rats and mice

Tamihiro Kawakami<sup>1</sup>, Haruki Shida<sup>2</sup>, Daigo Nakazawa<sup>2</sup>, Utano Tomaru<sup>3</sup>, Akihiro Ishizu<sup>4</sup>

<sup>1</sup>Department of Dermatology, St. Marianna University School of Medicine, Kawasaki, Japan, <sup>2</sup>Faculty of Health Sciences, Hokkaido University, Sapporo, Japan, <sup>3</sup>Department of Internal Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan, <sup>4</sup>Department of Pathology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Conflict of interest: None

**Objectives** We measured serum anti-phosphatidylserine-prothrombin complex (anti-PSPT) antibody levels in env-pX rats. We produced rat anti-PSPT antibody with mouse cross-reactivity and investigated the reaction of anti-PSPT antibody in the nude mouse. **Methods** We produced monoclonal antibodies against the rat PSPT antigen using hybridoma technology. Cross-reactivity of the produced rat anti-PSPT monoclonal antibodies was assessed in the mouse and human. Nude mice were intraperitoneally injected with the produced rat anti-PSPT antibody. Results Serum levels of both the IgG and IgM anti-PSPT antibody were significantly higher in the env-pX rats compared to those of WKAH wild type rats. Serum IgG anti-PSPT antibody levels in env-pX rats with cutaneous vasculitis were significantly higher than those of env-pX rats without cutaneous vasculitis. We provided a monoclonal antibody specific for rat anti-PSPT antibody by establishing a stable hybridoma. These IgM anti-PSPT monoclonal antibodies showed high cross-reactivity in the mouse but not human. The mice died due to heart mass congestion and pulmonary embolism. **Discussion** We believe we have established the first novel monoclonal anti-PSPT antibodies that induce thrombosis in the mouse in vivo.

## W25-2

### Pathogenicity of anti-lactoferrin antibody

Haruki Shida<sup>1</sup>, Daigo Nakazawa<sup>1</sup>, Utano Tomaru<sup>3</sup>, Tamihiro Kawakami<sup>4</sup>, Tatsuya Atsumi<sup>1</sup>, Akihiro Ishizu<sup>2</sup>

<sup>1</sup>Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, <sup>2</sup>Faculty of Health Sciences, Hokkaido University, <sup>3</sup>Department of Pathology, Hokkaido University Graduate School of Medicine, <sup>4</sup>Department of Dermatology, St. Marianna University

Conflict of interest: None

**Background.** Lactoferrin (LF) is one of the antigens of ANCA. However, the frequency or pathogenicity of anti-lactoferrin antibody (aLF) is elusive. Recently, it was reported that LF could act as an endogenous inhibitor of neutrophil extracellular trap (NET) formation. On the other hand, an excessive NET formation is involved in the pathogenesis of ANCA-associated vasculitis (AAV). **Objective.** To clarify the frequency of aLF in AAV, and to determine the pathogenicity. **Methods.** 65 sera from AAV patients (MPA: 45, EGPA: 19, GPA: 5) were enrolled for aLF detection. Neutrophils from healthy donors were cultured with suboptimal dose of PMA with aLF. Thereafter, NET formation was evaluated by DAPI staining. **Results.** 4 out of 65 sera (6.2%) were positive for aLF. All of them were EGPA sera. The frequency was 21%(4/19) in EGPA. In EGPA, BVAS of patients with aLF was significantly higher than that of patients without aLF ( $p<0.01$ ). The titer of aLF was correlated with BVAS ( $r=0.67$ ). NETs were poorly induced by stimulation with aLF alone or 10nM PMA. On the contrary, the amount of NETs induced by

stimulation with 10nM PMA and aLF was significantly greater than that with PMA and control IgG. **Conclusion.** aLF could accelerate NET formation and contribute to the disease activity in EGPA patients.

## W25-3

### A role of NETs in ANCA associated vasculitis

Kanako Murakami, Yoshinori Komagata, Chimako Mori, Akiko Endo, Soko Kawashima, Hideki Shimizu, Noriko Ikegaya, Satoshi Hayakawa, Kazuhito Fukuoka, Miho Karube, Akira Yamada, Shinya Kaname, Yoshihiro Arimura

1st Department of Kyorin University School of Medicine

Conflict of interest: None

**[Objectives]** It has been known that NETs are implicated in the pathogenesis of SLE and ANCA associated vasculitis (AAV). We reported the difference of NETosis by neutrophils from AAV patients and healthy controls (HC) in this congress last year. Here we observed NETs formation by neutrophils from HC and AAV patients before/after the treatment in order to investigate the role of NETs in AAV. We also determined the effects of NETs to Human Renal Glomerular Endothelial Cells (HRGECs). **[Methods]** Polymorphonuclear leukocyte (PMN) from HC were primed with phorbol myristate acetate (PMA) and incubated. The percentage of NETs producing cells were calculated. PMN were co-cultured with HRGECs with/without PMA and the amount of HRGECs injury were determined by ELISA. **[Results]** Activated PMN produced two types of NETs. One was fiber type and the other was non-fiber type. PMN from AAV patients before the treatment produced much more Fiber-NETs than HC. This fiber had different shape from that from HC neutrophils and was not detected after initial treatment. PMN from HC with PMA damaged HRGEC more than AAV patients. **[Conclusion]** It may be implicated that Fiber-NETs are involved in pathogenesis of AAV. HRGEC injury may be caused not only by NETs but also other factors.

## W25-4

### Clinical study of patients with anti-GBM disease experienced in single center

Noriko Ikegaya, Ikuho Kataoka, Takayuki Takahashi, Akiko Endo, Aya Sato, Sayaka Kubota, Masaki Saito, Soko Kawashima, Hideki Shimizu, Satoshi Hayakawa, Hitoshi Koji, Kazuhito Fukuoka, Miho Karube, Ken Yoshihara, Yoshinori Komagata, Akira Yamada, Shinya Kaname, Yoshihiro Arimura

First Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

Conflict of interest: None

**[Objectives]** We studied clinical features of anti-GBM disease patients experienced in single center for the last 30 years. **[Methods]** Eleven patients with anti-GBM disease diagnosed from January 1984 to April 2014 in Kyorin University Hospital was examined, retrospectively. **[Results]** The average age was 61.8 years old, five males and six females. Six patients (55%) had smoking histories. Four patients had pulmonary hemorrhage. In two patients, RPGN preceded pulmonary hemorrhage. Fever was seen as a first symptom in 73% of these patients. General symptoms, such as appetite loss, general malaise, muscular pain and arthralgia were also found. Laboratory data showed macroscopic hematuria in 27%. The median level of serum creatinine, CRP, anti-GBM anti-GBM antibody at the start of treatment, was 8.48 mg/dl, 15.9 mg/dl, 282.4 U/ml, respectively. After the treatments, 1 patient died of pulmonary hemorrhage, 2 patients recovered from renal failure (Group A), but 9 patients required maintenance hemodialysis (Group B). At the start of treatment, serum creatinine level was lower in group A than group B (2.58 mg/dl to 9.79 mg/dl). **[Conclusion]** In anti-GBM disease, early detection and therapy are closely related to kidney prognosis.

## W25-5

### A case of rapidly progressive glomerulonephritis exhibiting refractory increases of anti-GBM antibody

Daiki Yamazaki<sup>1</sup>, Akinori Yamaguchi<sup>1</sup>, Aiko Daigaku<sup>1</sup>, Mai Sugiyama<sup>1</sup>, Yasufumi Takahashi<sup>2</sup>, Kyoko Takahashi<sup>1</sup>, Tetsuji Kakegawa<sup>3</sup>, Yuji

Kamijo<sup>1</sup>

<sup>1</sup>Shinshu University Hospital, Nagano, Japan, <sup>2</sup>Shinshu Ueda Medical Center, Nagano, Japan, <sup>3</sup>Nagano Municipal Hospital, Nagano, Japan

Conflict of interest: None

A 43-year-old woman presented to her family clinic for fever and gross hematuria. Antibacterial agents were administered; however her clinical symptoms continued for two weeks. Laboratory and imaging analyses revealed the obvious acute kidney dysfunction (Cre 5.8mg/dl, UN 35mg/dl, proteinuria, hematuria, swelling of kidneys) with leukocytosis (WBC 9390/ $\mu$ l) and high inflammatory response (CRP 23mg/dl), then she transferred to our hospital for possibility of RPGN. At day1 after admission, intravenous steroid pulse therapy (mPSL pulse) was administered. At day6, anti-GBM antibody was detected with very high-titer (1110 U/ml). In addition to steroid therapy, hemodialysis (HD) and plasma exchange (PE) were introduced from day7, however the titer of the antibody was quickly rebounded. At day11, low-dose rituximab (RTX) (200mg) was administered, and additional mPSL pulse was done at day17. At day31, IVCY (500mg) was administered. Then, anti-GBM antibody gradually decreased and disappeared. Seventeen times of PE was performed, and it was finished at day47. She needed maintenance HD, but these treatments could prevent other serious complications. In this case report, we show a usefulness of multi-therapy including low-dose RTX and PE against refractory increases of anti-GBM antibody.

## W25-6

### Thrombotic microangiopathy caused by Heparin-induced thrombocytopenia accompanied with anti-glomerular basement membrane glomerulonephritis: two cases report

Yoshinobu Fuke, Seiichiro Hemmi, Mamiko Kajiwara, Takayuki Fujita, Masayoshi Soma

Department of Medicine, Division of Nephrology, Hypertension and Endocrinology, Nihon University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Case 1] A 54-year-old woman was administered hemodialysis (HD) and plasmaexchange for rapidly progressive renal failure due to anti-GBM glomerulonephritis (anti-GBMGN). At 11 hospital days, the platelet count (plt) decreased to  $7.5 \times 10^4$ /mL with positive for heparin-induced thrombocytopenia (HIT) antibody. Heparin was interrupted; however the thrombocytopenia progressively developed to  $2-5 \times 10^4$ /mL. Thrombotic microangiopathy (TMA) was defined by anemia, appearance of fragmented RBC, high serum LDH level and low haptoglobin level ( $<10$ mg/dl). A renal biopsy revealed crescent formations at glomeruli and thrombi at arch arteries, interlobular arteries and small vessels. [Case 2] A 60-year-old man was transferred to our hospital for severe renal impairment and continuous fever due to anti-GBMGN, who had been already treated with HD. At 5 hospital days, HIT caused thrombocytopenia ( $3.4 \times 10^4$ /mL) and thrombus at right iliac vein. Interruption of heparin could lead to soon recovery from the thrombocytopenia; however plt decreased to  $4-5 \times 10^4$ /mL at 45 hospital days again due to TMA. [Clinical significance] These two patients indicate that HIT accompanied with anti-GBMGN might play an important role in pathogenesis of TMA, leading to longstanding thrombocytopenia and severer renal impairment.

## W26-1

### Investigation on incomplete suppression of inflammation after first tocilizumab injection in polyarticular and oligoarticular juvenile idiopathic arthritis

Naomi Iwata, Mayuka Shiraki, Haruna Nakaseko, Shinji Kawabe  
Aichi Children's Health and Medical Center

Conflict of interest: None

[Objectives] There are some patients whose inflammation are not be suppressed after the first tocilizumab (TCZ) injection in polyarticular and oligoarticular juvenile idiopathic arthritis (JIA). The aim of this study was to assess the characteristics of the patients whose CRP did not become negative after the first TCZ injection. [Methods] The patients were classified in two groups by CRP at the fourth week after TCZ administra-

tion. The clinical data between two groups was compared (Age, Body weight, Previous treatment, serum markers, CRP, MMP-3). [Results] The CRP (+) group included 6 cases, and the CRP (-) group included 20 cases. In CRP (+) group and CRP (-) group, mean age was 7.2 years old and 11.8 years old, and mean body weight was 17.2 kg and 35.6 kg respectively. The age and body weight of the patients were significantly lower in JIA patients in CRP (+) group ( $p=0.04$ ,  $p=0.007$ ). In both groups, the number of patient with anti-CCP antibody was 3 cases (50%) and 14 cases (70%) respectively. The median CRP (mg/dl) was 2.6 and 0.68, and the median MMP-3 (ng/ml) was 193 and 315 respectively. Significant differences were not seen in two groups about CRP and MMP-3. [Conclusion] The patients with a light weight in JIA are less likely to be able to maintain blood concentration of TCZ.

## W26-2

### Computed Tomographycal evaluation of sacroiliatic joints for patients with juvenile ankylosing spondylitis treated with tumor necrosis factor inhibitors

Tomohiro Kubota<sup>1</sup>, Tsuyoshi Yamato<sup>1</sup>, Hiroyuki Wakiguchi<sup>1</sup>, Yukiko Nonaka<sup>1</sup>, Harumi Akaike<sup>1</sup>, Tomoko Takezaki<sup>1</sup>, Hiroyuki Imanaka<sup>1</sup>, Syuji Takei<sup>1,2</sup>

<sup>1</sup>Pediatric Medical Center, Kagoshima University Hospital, Kagoshima, Japan, <sup>2</sup>School of Health Sciences, Faculty of Medicine, Kagoshima University

Conflict of interest: None

[Background] Pelvis in children under growing period is susceptible to damage because of its vulnerability, however, there are few reports examined structural damage in children with juvenile AS (JAS). [Objectives] The aim of this study is to identify the factors that affect preservation of pelvis structure. [Patients/Methods] The patients were divided into two groups according to the structural damage in sacroiliac joints at the last visit: preserved group and progression group. The objective data are age at onset, gender, HLA typing, switching of TNFi and disease duration from onset to initiating biologic treatment. [Results] 6 JAS patients treated with TNFi were enrolled in this study. Patients initiated TNFi after 0.85 years (median, range 0.2~3) from their disease onset and were observed for 2.25 years (median, range 1.7~5.6). Destructions of sacroiliac joints were observed in two patients of 6, and the rest of 4 preserved their sacroiliac structures. There were no significant differences between two groups with respect to all objective data. However, all patients who initiated TNFi within one year from disease onset preserved their sacroiliac structures. [Conclusion] Early induction of TNFi agents may inhibit radiographic progression in sacroiliac joints in JAS patients.

## W26-3

### HBV vaccination for children with rheumatic diseases

Harumi Akaike<sup>1</sup>, Hiroyuki Wakiguchi<sup>1</sup>, Tsuyoshi Yamato<sup>1</sup>, Yuichi Yamasaki<sup>1</sup>, Tomohiro Kubota<sup>1</sup>, Yukiko Nonaka<sup>1</sup>, Yasuhito Nerome<sup>1</sup>, Tomoko Takezaki<sup>1</sup>, Hiroyuki Imanaka<sup>1</sup>, Syuji Takei<sup>1,2</sup>

<sup>1</sup>Department of Pediatrics, Children's Medical Center, Kagoshima University Medical And Dental Hospital, <sup>2</sup>Department of Maternal and Child Health Nursing School of Health Sciences, Faculty Medicine Kagoshima University

Conflict of interest: None

<Objective> To examine the sero-conversion rate and safety of HBV vaccine in patients with pediatric rheumatic diseases (PRD) <Patients and Methods> Children with PRD who were clinically in stable condition and were sero-negative for HBV (HBsAg, HBsAb, and HBeAb) were involved in the study. HBV vaccine was administered 3 times. Serum HBs Ab level was evaluated at 1 month after the last vaccination. <Result> A total of 37 PRD children were involved in the study; 27 JIA patients and 10 patients with collagen vascular diseases (6 patients with SLE, and a patient with JDM, SjS, MCTD, or PSS). Age at initial HBV vaccination was 16.7 years (median). The sero-conversion rate of HBsAb was 20/27 (74%) in JIA and that was 9/10 (90%) in collagen diseases. In JIA patients, seroconversion rate was age-dependent. HBs Ab levels were relatively lower in patients treated with biologic therapy. Of 111 episodes of HBV vaccination, skin reaction at injection site was observed in 6, tran-

sient joint pain in 3, and gastrointestinal symptom in 1. <Conclusion> HBV vaccination was useful to obtain preventive levels of HBVs Ab in PRD children. Considering that there were no severe adverse events or disease flare, HBV vaccination should be considered in PRD patients treated with immunomodulating therapy.

## W26-4

### Three cases of pediatric rheumatic disease who underwent surgery during treatment of biologic DMARDs

Kosuke Shabana<sup>1</sup>, Nami Okamoto<sup>1</sup>, Keisuke Shindo<sup>1</sup>, Takuji Murata<sup>1,2</sup>, Hiroshi Tamai<sup>1</sup>

<sup>1</sup>Department of Pediatrics, Osaka Medical College, Osaka, Japan, <sup>2</sup>Murata Kid's Clinic

Conflict of interest: None

[Objectives] To evaluate safety of surgery in pediatric rheumatic disease patients treated with biological disease-modifying anti-rheumatic drugs (bDMARDs). [Methods] We researched retrospectively 3 rheumatic disease children who were treated with bDMARDs. [Results] Case1 is 8-y-o boy of Behcet's disease. He was administered infliximab (5mg/kg every 7weeks) and was performed trabeculectomy (for glaucoma), exodontia (for erupted tooth) and placement of seton (for perirectal abscess). Case2 is 16-y-o girl of uveitis complicated with oligoarticular juvenile idiopathic arthritis (JIA). She was treated with infliximab (5mg/kg every 6weeks) and administered trabeculectomy (glaucoma) and intraocular lens implantation (for cataract). Case3 is 23-y-o female of systemic JIA. She was treated with tocilizumab (8mg/kg every 5weeks), and administered total hip arthroplasty. Similar to recommendation for surgery in adult patient treated with bDMARDs, all patients operated in a intermediate period between the scheduled dates of bDMARDs administration. In all patients, there was no adverse event, and they could continue bDMARDs after operation. [Conclusion] All patients safely underwent surgery and could continue bDMARDs. More investigation for other kinds of surgery and dDMARDs is needed.

## W26-5

### Comparison of the ACR classification criteria and the SLICC classification criteria in childhood systemic lupus erythematosus

Mayuka Shiraki, Haruna Nakaseko, Shinji Kawabe, Naomi Iwata  
Infection immune Department, Aichi Children's Health and Medical Center, Aichi, Japan

Conflict of interest: None

[Introduction] For the diagnosis of systemic lupus erythematosus (SLE), the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (2012) was proposed in addition to the American College of Rheumatology (ACR) classification criteria (1997) in adult. [Objective] We aimed to compare the sensitivity and specificity of the new SLICC criteria with those of the ACR criteria in our childhood-onset SLE patients. [Methods] Cases were the SLE patients who were younger than 18 year of age and admitted to our hospital between January 2003 and July 2014. Controls were patients with other rheumatic diseases who admitted between January 2008 and December 2013. The features were retrospectively reviewed. [Results] Both set of classification criteria were analysed in 51 SLE patients and 23 controls (Juvenile dermatomyositis 9, Mixed connective tissue disease 5, Sjogren's syndrome 9). The mean age of SLE patients was 11.6 years and the mean period from onset to diagnosis was 4.2 months. The sensitivity and specificity of the ACR criteria were 90.2% and 95.7%, respectively, whereas those of the SLICC criteria were 100% and 91.3%, respectively. [Conclusion] In our population, the SLICC criteria showed better sensitivity than the ACR criteria. The specificity were about the same.

## W26-6

### Clinical features of silent lupus nephritis in children

Hiroyuki Wakiguchi<sup>1</sup>, Tomohiro Kubota<sup>1</sup>, Tsuyoshi Yamato<sup>1</sup>, Akinori Miyazono<sup>1</sup>, Yukiko Nonaka<sup>1</sup>, Harumi Akaike<sup>1</sup>, Yasuhiro Nerome<sup>1</sup>, Tomoko Takezaki<sup>1</sup>, Hiroyuki Imanaka<sup>1</sup>, Syuji Takei<sup>1,2</sup>, Yoshifumi Kawano<sup>1</sup>

<sup>1</sup>Department of Pediatrics, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan, <sup>2</sup>School of Health Science, Faculty of Medicine, Kagoshima University, Kagoshima, Japan

Conflict of interest: None

[Objectives] To examine clinical and renal pathologic findings in children with silent lupus nephritis (sLN). [Methods] SLE patients whose onset was before 16 years old, referred to our hospital between 2000 to 2011, were recruited in the study. Patients were divided into two groups according to urinary findings at the first examination; overt LN (oLN) and sLN. Clinical findings such as gender, ISN pathologic classification, urinary findings after 3 years of therapy were retrospectively examined and compared between the two groups. [Results] A total of 31 SLE patients were involved in the study. Of the 31 patients, 13 (42%) were oLN and 18 (58%) were sLN. As to gender, the incidence of male was statistically higher in sLN (33%) group than oLN group (0%) (p=0.020). Pathologic findings of ISN classification in oLN patients was Class II in 3, III in 6, IV in 2, V in 1, and III+V in 1. In sLN patients, that was Class I in 3, II in 12, and III in 3. Urinary findings were still normal in 17/18 (94%) of sLN patients after 3 years of therapy. [Conclusion] Considering the general concept that the prognosis of SLE in male is more severe than that of female's, the present study may indicate that the early therapeutic intervention is essential to prevent the progression of renal damage.

## W27-1

### Clinical features in combined pulmonary fibrosis and emphysema (CPFE) with connective tissue diseases (CTD)

Takaaki Ishida<sup>1</sup>, Takeshi Shoda<sup>1</sup>, Kenichiro Hata<sup>2</sup>, Shuzo Yoshida<sup>1</sup>, Takuya Kotani<sup>1</sup>, Tohru Takeuchi<sup>1</sup>, Shigeki Makino<sup>1</sup>, Toshiaki Hanafusa<sup>1</sup>

<sup>1</sup>First Department of Internal Medicine, Osaka Medical College, Osaka, Japan, <sup>2</sup>Department of Internal Medicine and Connective Tissue Diseases, Yodogawa Christian Hospital, Osaka, Japan

Conflict of interest: None

[Objectives] We evaluated the clinical features in Combined pulmonary fibrosis and emphysema (CPFE) with CTD. [Methods] The patients who had interstitial pneumonia (IP) and emphysema by chest HRCT with rheumatoid arthritis (RA), dermatomyositis (DM), ANCA associated vasculitis (AAV), and scleroderma (SSc) were enrolled into this study. We assessed clinical features and prognosis retrospectively. [Results] Mean age was 68.4±9.4 years old (78 male, 38 female). 61 patients were RA-CPFE, 13 patients were DM-CPFE, 19 patients were AAV-CPFE, and 23 patients were SSc-CPFE. %FVC and %DLco/VA were lower in DM-CPFE and SSc-CPFE compared with AAV-CPFE and RA-CPFE, and FEV1.0% was higher. 17 patients of all diagnosed with lung cancer, and 23 patients died by exacerbation of IP (n=12), infection (n=4), and others (n=7). The median survival time was 12.5±1.1 years. The 3, 5, and 10 year survival rates were 89.9%, 75.3%, and 66.5%. Patients with SSc-CPFE had a good outcome, but then with DM-CPFE had a poor outcome. [Conclusion] Patients with CTD-CPFE were seen more prevalently in male patients and low pulmonary diffusing capacity at spirometry. SSc-CPFE had a good outcome.

## W27-2

### Features of sleep apnea syndrome in patients with established rheumatoid arthritis

Tomoyuki Mutoh, Yasuaki Okuda, Sho Mokuda, Yosuke Murata, Naoya Sawada, Akihiro Yamada, Kenichiro Matoba, Kazuo Jouyama, Makoto Onishi, Kiyoshi Takasugi

Center for Rheumatic Diseases, Dohgo Spa Hospital, Ehime, Japan

Conflict of interest: None

[Objectives] There have been several reports about the existence of sleep apnea syndrome (SAS) in patients with established rheumatoid arthritis (RA) so far. Here we investigated the relationship between SAS and the disease activities as well as functional disorders of these patients. [Methods] Polysomnographic studies were undertaken in 37 patients with established RA, and the severity indicators of SAS, such as respiratory



disturbance index (RDI) and 3% oxygen desaturation index (3%ODI) were measured. [Results] The average age of the participants was 75.7 years with the average disease duration of 24.6 years. Ten (27%) of them had moderate to severe sleep breathing disorder ( $20 \geq RDI$ ). In 3%ODI study, 32.4%(12 cases) showed the desaturation index of more than 15. Simple regression analysis revealed a positive relationship between RDI and HAQ-DI levels ( $r=0.433$ ,  $p=0.007$ ). All the patients with higher RDI (over 20) tended to show higher HAQ-DI score of more than 2. [Conclusion] Approximately 30% of established RA patients have been suffering from moderate to severe SAS and HAQ-DI levels were much higher in cases complicated with SAS. We propose the screening study with polysomnography should be undertaken on patients with high HAQ-DI levels, since concomitant rate of SAS was high.

### W27-3

#### The Prognostic factor in 56 Patients with Myositis-associated Interstitial Lung Disease

Akira Shiraki

Department of Respiratory Medicine, Ogaki Municipal Hospital, Ogaki, Japan

Conflict of interest: None

[Objectives] To evaluate the prognosis markers in patients with ILDs associated to PM/DM. [Methods] We reviewed clinical (C-reactive protein, Krebs von den Lungen-6, anti-ARS-abs, anti-MDA5-ab, lymphocytes in bronchial lavage, amyopathic DM) and radiological data of the 51 consecutive patients with ILDs related to PM/DM, retrospectively. Anti-ARS-abs and anti-MDA5-ab were screened out by immunoprecipitation techniques in Department of Dermatology, Kanazawa University and ELISA method in Department of Dermatology, Nagoya University. [Results] Median age was 61 years old and DM was 64.3%. 24 patients (42.9%) had anti-ARS-abs and 10 patients (17.9%) had anti-MDA5 ab. Median follow up period was 3.0 years. Anti-ARS-abs positive ( $p=0.025$ ) and anti-MDA5-ab positive ( $p=0.004$ ) were significant factors between 1 year survivors and non-survivors. C-reactive protein (CRP)  $> 1.0$  ( $p=0.004$ ) was the only significant factor between overall survivors and non-survivors. [Conclusion] Anti-MDA5-ab was a risk factor on short-term survivals and CRP value was related to long-term prognosis in this cohort.

### W27-4

#### Today's situation of treatment selection of Rheumatoid arthritis(RA) patients associated with interstitial pneumonia(IP) of our institute

Shigeki Makino, Takeshi Shoda, Takuya Kotani, Shuzo Yoshida, Tohru Takeuchi, Toshiaki Hanafusa

1st Department of Internal Medicine, Osaka Medical College, Osaka, Japan

Conflict of interest: Yes

[Objectives] Because of many therapeutic restrictions, RA-IP patients are placed in bad controlled state. We aim to know treatment selections and management conditions of patients with RA-IP. [Methods] We reviewed clinical data concerning treatment and DAS28CRP of our RA patients in September 2014. [Results] Total RA patients were 711 (153 males). Among them, RA-IP patients (IP group) are 89 (41 males), RA without IP patients (non IP group) were 622 (112 males). MTX, Corticosteroid, Biologics, Tacrolimus, SASP and Bucillamin are prescribed for 19%, 61%, 27%, 56%, 28%, 10% of IP group patients, and 67%, 30%, 26%, 14%, 28%, 14% of non IP group patients. Remission rate and LDA rate in DAS28CRP are 61%, 20% of IP group patients, and 64%, 11% of non IP group patients. [Conclusion] In the treatment of RA-IP patients, we avoid MTX and preferred corticosteroid and tacrolimus. There is no difference between management condition of IP group patients and those of non IP group patients.

### W27-5

#### Usage survey on biologic DMARDs for patients with rheumatoid arthritis complicated with respiratory comorbidity

Takahiro Seno<sup>1,2</sup>, Risa Sagawa<sup>2</sup>, Aiko Tominaga<sup>2</sup>, Takashi Kida<sup>2</sup>, Yuji

Kukida<sup>2</sup>, Hidetake Nagahara<sup>2</sup>, Wataru Fujii<sup>2</sup>, Ken Murakami<sup>2</sup>, Aihiro Yamamoto<sup>2</sup>, Ryo Oda<sup>3</sup>, Toshikazu Kubo<sup>1,3</sup>, Masataka Kohno<sup>2</sup>, Yutaka Kawahito<sup>2</sup>

<sup>1</sup>Department of Rheumatic Diseases and Joint Function, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>2</sup>Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>3</sup>Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: Yes

[Objectives] We show the usage of biologic DMARDs for patients with rheumatoid arthritis (RA) complicated with respiratory comorbidity. [Methods] We extract patients with RA who were complicated with respiratory comorbidity from our outpatient database. And we research some parameters; disease name, biologic DMARDs, non-biologic DMARDs, disease activity. [Results] We analyzed 53 RA patients with respiratory comorbidity. 23 patients were interstitial lung disease (ILD), and 10 of them were treated with etanercept (ETN), 8 were with abatacept (ABT), and 5 were with tocilizumab (TCZ). On the other hand, about non-biological DMARDs, PSL (12/23 patients), tacrolimus (8/23 patients) and salazosulfapyridine (SASP) (4/23 patients) were predominantly used for ILD patients. 2 patients were mycobacterium infection, all the patients were treated with ABT and SASP. 8 patients were complicated with bronchiectasis, 6 of them were used ABT and 4 were treated with MTX. In those cases, bronchiectasis might be considered as respiratory tract involvement of RA. [Conclusion] MTX was avoided for ILD patients, and ETN, ABT and TCZ were mainly used. ABT was predominantly used for respiratory tract comorbidity. Biologic DMARDs usage is depending on the condition of pulmonary disease.

### W27-6

#### Estimation of clinical features and cytokine profile in RA patients with bronchial asthma and eosinophilic sinusitis

Hiroshi Ishida

Ishida RA Clinic

Conflict of interest: None

[Objectives] To explore the clinical features and serum cytokine profile in RA patients accompanied with bronchial asthma (BA) and eosinophilic sinusitis (ES), these RA patients and non-combined 5 BA nor ES control RA patients are compared from clinical aspects and cytokine profile pattern in sera. [Methods] Patients with BA diagnosed by qualified respiratory physician based on spirometry and CT, and ES diagnosed by qualified nasal allergologist based on nasal endoscopy, nasal discharge analysis, and CT are selected 5 RA patients. Controlled RA patients are choiced age, sex, disease duration, class, stage, DAS28 score, TSS matched with BA & ES combined RA patients. Both groups are carefully observed and checked from clinical aspects and various cytokine levels are assayed by specific sandwich-ELISA. [Results] BA & ES combined RA group is less extrajoint symptoms such as interstitial pneumonia and RA nodule than control group. Target group is anti-CCP antibody negative. Serum IL-10 in target iRA patients is lower than that in control patients, however TNF and IL-6 is no significant difference. Steroid inhalation and nasal flow out is effective for ES. [Conclusion] Collectively, BA patients with ES are already reported, but RA with both airway disease is a new subset of classical RA.

### W28-1

#### The efficacy of immunosuppressive therapy for pulmonary arterial hypertension associated with connective tissue disease (CTD-PAH)

Yusuke Takeshima<sup>1</sup>, Yukiko Iwasaki<sup>1</sup>, Rika Kato<sup>1</sup>, Shuji Sumitomo<sup>1</sup>, Harumi Shirai<sup>1</sup>, Bunki Natsumoto<sup>1</sup>, Mineto Ota<sup>1</sup>, Shuzo Teruya<sup>1</sup>, Haruka Tsuchiya<sup>1</sup>, Toshihiko Komai<sup>1</sup>, Norio Hanata<sup>1</sup>, Hirofumi Shoda<sup>1</sup>, Mihoko Shibuya<sup>1</sup>, Hisataka Maki<sup>2</sup>, Masaru Hatano<sup>2</sup>, Keishi Fujio<sup>1</sup>, Kazuhiko Yamamoto<sup>1</sup>

<sup>1</sup>Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, <sup>2</sup>Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Conflict of interest: None

Association of CTD is one of the poor prognostic factors for PAH patients. Here we report clinical courses of 6 cases under immunosuppressive therapy for CTD-PAH with some literature review. **[Case1]** A 44-year-old woman with overlap syndrome of SLE and CREST syndrome for 16 years was initially treated with vasodilators and high-dose PSL. Intravenous CY (IVCY) was discontinued, because of cholangitis. Upon exacerbation of PAH one year after the treatment, high-dose PSL and resumption of IVCY improved PAH. **[Case2]** A 32-year-old woman with SLE for 7 years showed well improvement of PAH by high-dose PSL and IVCY. Six months later, PAH relapsed and a PDE5-inhibitor was started. **[Case3]** A 33-year-old woman with MCTD for 16 years was diagnosed with PAH 4 years ago. She was treated with vasodilators. One month after the administration of high-dose PSL and CyA for pancytopenia, PAH improved. She proceeded in IVCY. **[Case4-6]** 3 cases of PAH with Sjögren syndrome were treated with PSL. All cases improved and stay on treatment with IVCY. **[Clinical significance]** High-dose PSL and IVCY are effective to all cases, indicating the importance of the immune system in CTD-PAH etiology. In case 2, B-cell reduction in PBMC was apparent after IVCY, suggesting that B-cell count may predict activity.

## W28-2

### Immunosuppressive therapy in pulmonary hypertension associated with connective tissue diseases

Yoshioki Yamasaki, Kosei Tsuchida, Yusa Tajima, Hirofumi Mitomi, Hisae Ohjimi, Teisuke Uchida, Seido Ooka, Takahiro Okazaki, Shoichi Ozaki, Hidehiro Yamada  
Rheumatology and Allergology, St. Marianna University School of Medicine

Conflict of interest: Yes

**[Objectives]** To analyze the efficacy of immunosuppressants (IS) in pulmonary hypertension (PH) in connective tissue diseases (CTD). **[Methods]** Ten patients with CTD-associated PH were treated with IS since 2010. Of them, we analyzed 7 patients who had more than half year of the observation period. Patients with PH who did not need or could withdraw some pulmonary vasodilator, or who was improved only by IS were considered as responders. **[Results]** Two patients with MCTD, 2 with SLE, 1 with primary SjS, 1 with anti-RNP-positive SSc / SLE, and 1 with anti-centromere-positive SSc / SjS were included. Mean follow-up period (SD) were 26 (15) months. One, 4, and 2 had WHO-FC I, II, IV, respectively. Pulmonary vascular resistance (PVR) (IQR) was 389 (360-538) dyn.sec.cm<sup>-5</sup>. Along with steroid (more than moderate), cyclophosphamide (5 patients), azathioprine (1), and tacrolimus (1) were introduced. Six of 7 patients were responders. Five of 6 had an improved WHO-FC (another one had WHO-FC I at baseline). PVR (IQR) reduced to 248 (123-299) dyn.sec.cm<sup>-5</sup> (P = 0.013). One non-responder had SSc / SjS with PH (WHO-FC IV) carrying anti-centromere. This patient had improved PVR but later developed left heart failure. **[Conclusion]** PH might have response to IS therapy even among some patients with SSc.

## W28-3

### Prognostic factors of pulmonary hypertension in patients with connective tissue diseases

Mizuki Yagishita, Hiroshi Ogishima, Hidenori Takahashi, Izumi Kurata, Saori Abe, Hiroshi Ebe, Hiroyuki Takahashi, Yuko Kurashima, Masahiro Yokosawa, Tomoya Hirota, Hiromitsu Asashima, Shinya Hagiwara, Naoto Umeda, Yuya Kondo, Hiroto Tsuboi, Takeshi Suzuki, Isao Matsumoto, Takayuki Sumida  
Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

Conflict of interest: None

**[Objectives]** To evaluate prognostic factors of pulmonary hypertension in patients with connective tissue diseases. **[Methods]** Eight patients (SLE or SSc) diagnosed with PH from 2010 to 2014 were divided into two groups; treatment-response group (max TRPG decreased less than 40 mmHg) and treatment-resistant group. We analyzed the relationship between responsiveness to treatment and prognostic factors including

underlying diseases, autoantibodies and treatment. **[Results]** 1) Both treatment-response group and treatment-resistant group included four patients. 2) Max TRPG before the treatment had no significant difference between two groups ( $63 \pm 20$  vs  $75 \pm 6.8$  mmHg,  $p = 0.18$ ), but that after the treatment more likely to decrease in the former ( $40.2 \pm 18$  vs  $10.5 \pm 14$  mmHg,  $p = 0.07$ ). 3) The former included three patients with SLE and one SSc patient. 4) The latter included one patient with SLE and three SSc. 5) Anti-RNP antibody was positive among 25% of the former and 100% of the later, significantly higher in treatment-resistant group ( $p = 0.03$ ). **[Conclusion]** SLE was more likely to respond to the treatment than SSc. The positive rate of anti-RNP antibody was significantly higher in the treatment-resistant group, suggesting the relationship between anti-RNP antibody and treatment resistance.

## W28-4

### A study of CTD-PAH exacerbation

Shusaku Nakashima, Risa Wakiya, Hiroki Ozaki, Hiromi Shimada, Yohei Takeuchi, Miharu Izumikawa, Tomohiro Kameda, Kentaro Susaki, Hiroaki Dobashi  
Department of Internal Medicine, Division of Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University, Kagawa, Japan

Conflict of interest: None

**(Objectives)** CTD-PAH had a lower survival rate compared with IPAH before. However, the prognosis in CTD-PAH is improving by changed strategy of diagnosis and treatment. CTD-PAH is categorized in one of the PAH in *Nice* classification and we treat under idiopathic pulmonary hypertension (IPAH) guidelines. The efficacy of the immunosuppressive therapy of the CTD-PAH is not established though some reports describe that early intervention is effective. We consider treatment strategy for CTD-PAH by examining exacerbation of CTD-PAH patient treated in our facility. **(Methods)** We investigated 15 CTD-PAH patients treated in our facility. We defined the exacerbation as WHOFC becoming worse. We surveyed background, underlying disease, cause worsening, treatment; pulmonary vasodilator, immunosuppressive therapy in CTD-PAH patient. **(Results)** Five of 15 CTD-PAH patients (SSc3, SLE1, MCTD1) turned worse. Pulmonary vasodilator therapy was conducted in all case. Immunosuppressive therapy was conducted four of five patients. A cause worsening of CTD-PAH is Progress of PAH, PVOD and pericardial fluid retention. **(Conclusion)** In this examination, there was various cause of CTD-PH exacerbation. Because the causes of CTD-PH are various, we must strengthen treatment after evaluating a cause of worsening.

## W28-5

### A longitudinal study of arteriosclerotic vascular change in Connective tissue diseases

Harumi Kuda<sup>1</sup>, Mari Ushikubo<sup>1</sup>, Keisuke Izumi<sup>2</sup>, Kumiko Akiya<sup>1</sup>, Ikuko Tanaka<sup>3</sup>, Shigenori Tamaki<sup>3</sup>, Hisaji Oshima<sup>1</sup>  
<sup>1</sup>Tokyo Medical Center, <sup>2</sup>Division of Rheumatology, Keio University School of Medicine, <sup>3</sup>Nagoya Rheumatology Clinic

Conflict of interest: None

**[Objectives]** To investigate the influence of disease activity, steroid through the longitudinal study disease to atherosclerotic vascular changes in connective tissue diseases. **[Methods]** Carotid artery ultrasonography and were able to observe the elapsed to transition more than 2 years perform pulse tests were directed to 39 cases of collagen disease patients than rheumatoid arthritis. Age  $62 \pm 10$  years (mean $\pm$ SD), women 35 cases, the observation period is  $37 \pm 13$  months, steroid usage  $PSL5.9 \pm 4.6$  mg/day, total steroid amount of  $47 \pm 39$  g, systemic lupus erythematosus is 18 cases. Carotid ultrasound (IMT), heart ankle blood vessel elasticity index (CAVI), to measure the ankle brachial index (ABI). **[Results]** 1) observed at the start of the IMT, ABI, CAVI each  $0.74 \pm 0.14$  mm, was  $1.12 \pm 0.05$ ,  $8.46 \pm 1.37$ . 2) the average amount of change per year during the observation period (/year) IM  $0.04 \pm 0.05$ , ABI is  $-0.02 \pm 0.07$ , CAVI was  $0.07 \pm 0.45$ . 3) the amount of change in IMT did not show a significant correlation with BMI, CAVI and steroids amount. On the other hand, the amount of change in ABI was negatively correlated with the total steroid dose ( $<0.05$ ). **[Conclusion]** The atherosclerotic vascular changes in con-

nective tissue diseases, in addition to the risk factors, the influence of steroids has also been suggested.

## W28-6

### Serum adipokine level is associated with progression of atherosclerosis in systemic autoimmune diseases undergoing glucocorticoid therapy

Shotaro Masuoka, Nahoko Tanaka, Natsuko Kusunoki, Tatsuhiro Yamamoto, Kaichi Kaneko, Sei Muraoka, Makoto Kaburaki, Kotaro Shikano, Natsuki Fujio, Hiroshi Sato, Mai Kawazoe, Emiko Shindo, Kenji Takagi, Tomoko Hasunuma, Shinichi Kawai  
Division of Rheumatology, Department of Internal Medicine, School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan

Conflict of interest: None

[Objectives] We investigated the association of adipokines and glucocorticoid (GC) therapy with premature atherosclerosis in patients with systemic autoimmune diseases. [Methods] Thirty eight patients with systemic autoimmune diseases who had started GC therapy were enrolled. The carotid arteries were examined by ultrasonography to detect premature atherosclerosis at initiating GC therapy and after mean 3.4 years. Serum levels of adipokines [resistin (RS), leptin (LP), and high molecular weight adiponectin (HMW-AD)] were measured with enzyme-linked immunosorbent assay kits. [Results] The median value of the maximum intima-media thickness (IMT) was increased from 0.675 (IQR 0.500-0.813) mm to 0.725 (0.588-0.725) mm ( $p = 0.04$ ). Serum RS levels decreased, while serum LP and HMW-AD levels increased after GC therapy. Average yearly change in IMT was positively associated with hypertension, diabetes mellitus and history of cardiovascular events, and also with the yearly change in serum RS levels. While average yearly change in IMT was negatively associated with cumulative prednisolone. [Conclusion] Premature atherosclerosis might be positively related to the serum RS level, while it might be negatively related to GC therapy in patient of systemic autoimmune diseases.

## W29-1

### The causes of death in deceased patients with RA using NinJa 2013 cohort

Atsushi Kaneko<sup>1</sup>, Toshihiro Matsui<sup>2,4</sup>, Daihei Kida<sup>1</sup>, Yosuke Hattori<sup>1</sup>, Hiroyasu Kanda<sup>1</sup>, Shigeto Tohma<sup>3,4</sup>  
<sup>1</sup>Dept. of Orthop. Surg. And Rheumatology, Nagoya Medical Center, National Hospital Organization, <sup>2</sup>Department of Rheumatology, Sagamihiro National Hospital, Kanagawa, Japan, <sup>3</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihiro National Hospital, NHO, Kanagawa, Japan, <sup>4</sup>iR-net

Conflict of interest: None

[Objectives] The purpose of the present study is to evaluate the age at death and the cause of death in patients with rheumatoid arthritis (RA) in 2013. [Methods] 118 Japanese deceased patients with RA, who were registered in the large cohort database (NinJa: National Database of Rheumatic Diseases by iR-net in Japan). We investigated the age at death, the causes of death of all patients. [Results] The mean age at death was 74.1 years old. The major cause of death in deceased patients was infection in 34 patients involving in pneumonia in 15 patients. Next was malignancy in 20 patients, respiratory dysfunction involving intestinal pneumonia in 18 patients, cardiovascular disease in 17 patients. [Conclusion] The life expectancy of Japanese patients with RA was getting better. But the major causes of death were still infection involving in bacterial or viral or pneumonia, opportunistic infection.

## W29-2

### Biologics do not increase risk for malignancy in Japanese patients with rheumatoid arthritis – an interim analysis of SECURE study

Masayoshi Harigai<sup>1,2</sup>, Ryoko Sakai<sup>1,2</sup>, Michi Tanaka<sup>1,2</sup>, Fumio Hirano<sup>1,2</sup>, Waka Yokoyama<sup>1,2</sup>, Kenji Nagasaka<sup>1,2</sup>, Ryuji Koike<sup>1,2</sup>, Takao Koike<sup>3</sup>, Nobuyuki Miyasaka<sup>2</sup>

<sup>1</sup>Department of Pharmacovigilance, Tokyo Medical and Dental University, <sup>2</sup>Department of Rheumatology, Tokyo Medical and Dental University, <sup>3</sup>NTT East Sapporo Hospital

Conflict of interest: Yes

**Objectives:** To investigate risk for malignancy in Japanese patients with rheumatoid arthritis (RA) treated with biologics. **Methods:** 14,440 Japanese patients with RA who ever used biologics were registered to the SECURE study. Age-standardized incidence rate (ASIR) and standardized incidence ratio (SIR) of malignancy were calculated using Japanese general population in 2002 as a reference. **Results:** Demographics at baseline were as follows: female, 81%; mean age at the start of the first biologic, 57.0 years; mean observation period, 41.1 months. Of 333 malignancies reported, 258 were non-hematological and 72 were malignant lymphoma. ASIR for all malignancies was 313.9 while the estimated incidence rate of malignancy in Japanese general population was 447.8/100,000 patient-years. SIRs for all malignancies, non-hematological malignancies, and malignant lymphoma were 0.767, 0.613 and 6.579 for female and 0.701, 0.590 and 5.237 for male, respectively. **Conclusion:** Use of biologics did not increase the risk for over all malignancies in patients with RA compared to the Japanese general population. Although the SIRs for malignant lymphoma in SECURE cohort was elevated, they were similar to those reported from other cohorts of Japanese patients with RA.

## W29-3

### Prognostic Factors Predicting Mortality of Adult Still's Disease

Kazuhiro Uchiyama<sup>1</sup>, Hidekazu Ikeuchi<sup>1</sup>, Rena Motohashi<sup>2</sup>, Noriyuki Sakurai<sup>1</sup>, Toru Sakairi<sup>1</sup>, Yoriaki Kaneko<sup>1</sup>, Akito Maeshima<sup>1</sup>, Keiji Hiromura<sup>1</sup>, Yoshihisa Nojima<sup>1</sup>

<sup>1</sup>Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine, <sup>2</sup>Maebashi Red Cross Hospital

Conflict of interest: None

[Objectives] To explore prognostic factors for mortality of Adult Still's Disease (ASD) [Methods] We retrospectively analysed 27 ASD patients (8 males, 19 females) who admitted to our department from 1997 to 2013. [Results] The median age was 33.0 years (range, 15-64). The median follow-up period was 26 months (range, 5-170). The initial therapy was as follows; steroid pulse therapy in 8, oral steroid in 17 and NSAIDs alone in 2. During follow-up periods, 17 patients received immunosuppressants; methotrexate in 16, cyclosporine in 9, tacrolimus in 3 and cyclophosphamide in 1. Relapse was observed in 15 patients (55.5%). Five patients died (18.5%, multiple organ failure in 3, sepsis in 1, and respiratory failure in 1). All death occurred after relapse. The median interval between introduction of therapies to death was 38 months (range, 13-109). Compared to survivors, dead patients had lower hemoglobin levels (mean, 8.9 vs 11.3 g/dl,  $p=0.0176$ ), higher triglyceride levels (median, 294.0 vs 112.5 mg/dl,  $p=0.001$ ), and higher prevalence of hemophagocytic syndrome (HPS) (60% vs 9%,  $p=0.030$ ) and disseminated intravascular coagulation (DIC) (80% vs 18%,  $p=0.017$ ) before the initiation of therapy. [Conclusion] HPS and DIC at the disease onset were predictive factors for mortality of ASD.

## W29-4

### Risk factor for malignant lymphoma in patients with rheumatoid arthritis

Atsushi Hashimoto<sup>1</sup>, Noriyuki Chiba<sup>2</sup>, Jinju Nishino<sup>3</sup>, Toshihiro Matsui<sup>1</sup>, Shigeto Tohma<sup>4</sup>

<sup>1</sup>Department of Rheumatology, Sagamihiro National Hospital, National Hospital Organization, Kanagawa, Japan, <sup>2</sup>Department of Rheumatology, Morioka National Hospital, National Hospital Organization, Iwate, Japan, <sup>3</sup>Nishino Orthopedic Clinic, Tokyo, Japan, <sup>4</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihiro National Hospital, National Hospital Organization, Kanagawa, Japan

Conflict of interest: None

[Objectives] Patients with rheumatoid arthritis (RA) have higher incidence of malignant lymphoma (ML) than the general population. We attempted to identify the risk factor for ML. [Methods] Using the data of RA patients obtained from a nationwide multicenter Japanese cohort database 'NinJa' from 2003 to 2012, standardized incidence ratio (SIR) was calculated and the following background factors in the preceding year of developing ML were analyzed for the risk factors: age, sex, RA

disease duration, Steinbrocker stage score, global functional status, disease activity score in 28 joints (DAS28), and use of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, methotrexate (MTX), immunosuppressants, and biologics. **[Results]** In 66953 patient-years 63 patients developed ML, of which the SIR was significantly higher than the general population (3.43), while that of entire malignancies was not (0.89). Significant risk factors for ML were higher age (Odds ratio (OR) 1.4 per additional 10 years), use of MTX (OR 3.5) and use of tacrolimus (OR 3.9). **[Conclusion]** RA patients having such risk factor should be cared for developing ML. Analysis of accumulated disease activity of RA or dosing period of every medication could contribute to further investigation.

## W29-5

### The selection of Biologics - From NinJa Database-

Jinju Nishino<sup>1</sup>, Yuho Kadono<sup>2</sup>, Toshihiro Matsui<sup>3</sup>, Tetsuro Yasui<sup>2</sup>, Naoko Shoda<sup>2</sup>, Yasunori Omata<sup>2</sup>, Takuma Koyama<sup>2</sup>, Hiroyuki Oka<sup>5</sup>, Kumiko Ono<sup>2</sup>, Sakae Tanaka<sup>2</sup>, Shigeto Tohma<sup>4</sup>

<sup>1</sup>Department of Orthopaedic Surgery, The University of Tokyo Hospital, <sup>2</sup>Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, <sup>3</sup>Department of Rheumatology, Sagamihara Hospital Hospital, National Hospital Organization, <sup>4</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihara Hospital Hospital, National Hospital Organization, <sup>5</sup>22nd Century Research Center, The University of Tokyo Hospital

Conflict of interest: None

**[Objectives]** The aim of this study is the survey of factors affected to biologics selection. Subjects and **[Methods]** 342 rheumatoid arthritis patients newly prescribed biologics in 2013 were extracted from National database of Rheumatic disease by iR-net (NinJa). The background conditions for every biologics in 2012 were investigated. The short-term effect of every biologics were investigated by Propensity Score Matching methods. **[Results]** The factors affected biologics selection were Age, Physician's speciality, Steinbrocker's Stage, Comorbidities. We found no difference of effect among biologics. **[Conclusion]** The physician's selections of biologics for senile, established, poor-risk RA patients tend to non-TNF inhibitors.

## W29-6

### Prevalence and clinical features and risk factors associated with non-tuberculous mycobacteriosis in patients with rheumatoid arthritis -Analysis of NinJa 2013 database-

Masao Katayama<sup>1</sup>, Yasuo Suenaga<sup>2</sup>, Noriyuki Chiba<sup>3</sup>, Shiro Ohshima<sup>4</sup>, Shigeto Tohma<sup>5</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Nagoya Medical Center, National Hospital Organization, Nagoya, Japan, <sup>2</sup>Department of Rheumatology, Beppu Medical Center, National Hospital Organization, Oita, Japan, <sup>3</sup>Department of Rheumatology, Morioka Hospital, National Hospital Organization, Iwate, Japan, <sup>4</sup>Department of Clinical Research, Osaka-Minai Medical Center, National Hospital Organization, Osaka, Japan, <sup>5</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihara Hospital, National Hospital Organization, Sagamihara, Japan

Conflict of interest: None

**[Objectives]** In RA patients the epidemiologic data about non-tuberculous mycobacteriosis (NTM) are scarce. We aimed to analyze the prevalence and clinical features and risk factors associated with NTM in patients with RA using a large Japanese cohort database. **[Methods]** We investigated NTM prevalence rate in RA patients registered in NinJa database in 2012 and 2013. We surveyed associated other diseases, detecting bacterial species, chest radiographic findings, patient profiles and so on in the 2 year. **[Results]** By the reason of hospitalized diagnosis the patients associated with NTM by NinJa 2013 were 12/13,285 (90.3 cases/100,000 persons). And those by NinJa 2012 were 9/11,920 (75.4 cases/100,000 persons). Prevalence in NTM surveyed by questionnaire, which were replied by 12 facilities, were 751.2 cases/100,000 persons in 2012 and 971.1 cases/100,000 persons in 2013, both of which were remarkably high. Clinical features and risk factors such as MTX and bio-

logic agent therapy background and RA-specific lower respiratory tract lesions will be further investigated. **[Conclusion]** It is suggested that NTM prevalence rate in RA patients was remarkably high compared to prevalence rate in the general population by the examination using data from a large Japanese cohort database.

## W30-1

### Ultrasonography predicts the clinical response to biological agents in rheumatoid arthritis

Yuji Nozaki, Kenji Sakai, Shinkai Ri, Asuka Inoue, Chiemi Tasaki, Kayo Asato, Toshihiko Shiga, Tomohiro Yano, Shoichi Hino, Yasuaki Nagare, Masanori Funauuchi, Itaru Matsumura  
Department of Hematology and Rheumatology, Kindai University School of Medicine

Conflict of interest: None

**[Objectives]** To determine whether ultrasonography (US) predicts clinical response in rheumatoid arthritis (RA) who has treated with biological agents. **[Methods]** 53 RA patients (Female 48/man 5) were recruited with biological agent between 2010 and 2014. The mean duration of disease, age, and DAS28-CRP was 6.6 year, 55.3 years old, and 4.6 scores. We assessed the gray scale (GS; 0-4) and power doppler (PD; 0-1) in 28 joints by ultrasonography. We estimated the correlation of the GS/PD and DAS28, tender joint count (TJC), swollen joint count (SJC), CRP, and patient VAS in clinical response before and after biological agent treatment. **[Results]** Total GS, but not total PD, is correlated with DAS28-CRP, TJC, SJC, CRP, and Pt VAS at 54 weeks. Total GS at baseline in the RA patients who achieved the clinical remission (DAS28-CRP < 2.3) at 54 weeks was decreased significantly compared to that in patients who did not achieved the clinical remission ((DAS28-CRP ≥ 2.3). **[Conclusion]** We concluded the estimation of total GS by ultrasonography is useful tool by the reason that total GS was significant correlated with the disease activity in RA patients with biological agents. We also demonstrated that ultrasonography (US) predicts clinical response in RA who has treated with biological agents.

## W30-2

### Disease activity at 3 months predicts remission at one year in patients with early rheumatoid arthritis

Masahiro Minoda<sup>1</sup>, Hideto Oshikawa<sup>1</sup>, Naoho Takizawa<sup>1</sup>, Kenichiro Tokunaga<sup>1</sup>, Kazuki Yoshida<sup>2</sup>, Mitsumasa Kishimoto<sup>3</sup>, Kazuo Matsui<sup>1</sup>

<sup>1</sup>Kameda Medical Center, Chiba, Japan, <sup>2</sup>Harvard School of Public Health, <sup>3</sup>St. Luke's International Hospital, Tokyo, Japan

Conflict of interest: None

**[Objectives]** Remission has become a realistic goal in patients with early rheumatoid arthritis (RA). However how many and which patients can achieve remission are not well known. **[Methods]** The patients with early RA who visited Department of Rheumatology, Kameda Medical Center from January to September 2010 were included in this study. Inclusion criteria for eligible patients were age 18 years or older, disease duration less than 2 years and DMARDs naïve at first visit. We conducted retrospective chart review to investigate remission rate at one year and its predictive factors. **[Results]** Among 138 patients originally included, 102 patients could be followed at one year. Baseline characteristics include mean age 59.0 years, female 73%, mean disease duration 24.0 weeks and mean DAS28-ESR 4.41. The DAS28-ESR remission (<2.6) rate at one year was 62%. When compared with non-remission group, remission group had significantly low anti-CCP antibody (P=0.03), low ESR (p<0.01), low mHAQ (p=0.05) at baseline and low disease activity at 3 months (p<0.01). **[Conclusion]** In routine practice, 62% of early RA patients have achieved DAS28-ESR remission. Baseline characteristics and disease activity at 3 months were suggested as predictive of remission at one year.

### W30-3

#### Ultrasonography is a potent tool for the prediction of radiographic progression in the patients with rheumatoid arthritis treated with biological agents

Kenji Mamoto<sup>1</sup>, Tatsuya Koike<sup>2,3</sup>, Tadashi Okano<sup>1</sup>, Yuko Sugioka<sup>2</sup>, Masahiro Tada<sup>1</sup>, Kentaro Inui<sup>4</sup>, Hiroaki Nakamura<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Osaka City University Medical School, Osaka, Japan, <sup>2</sup>Center for Senile Degenerative Disorders (CSDD), Osaka City University Medical School, Osaka, Japan, <sup>3</sup>Search Institute for Bone and Arthritis Disease (SINBAD), Wakayama, Japan, <sup>4</sup>Department of Rheumatology, Osaka City University Medical School, Osaka, Japan

Conflict of interest: None

[Objectives] The aim of this study was to check whether the synovial power Doppler (PD) and gray scale (GS) ultrasound (US) scores could predict radiographic progression better than conventional measures in rheumatoid arthritis (RA) patients receiving biological agents (Bio). [Methods] One hundred and twenty seven patients with RA who had recently received Bio were enrolled. Patients underwent clinical, laboratory assessment at every 2 months from baseline to 12 months and US assessment at baseline, 6 and 12 months. The GS and PD signals were scored in 26 synovial sites (22 joints). Radiographic damage was evaluated using van der Heijde modified total Sharp score (TSS) at baseline and 12 months. [Results] Eighty one patients finished 12-months observation.  $\Delta$ TSS significantly correlated with total GS scores at baseline ( $\gamma=0.318$ ,  $\beta=0.342$ ,  $P<0.05$ ), total PD scores at baseline ( $\gamma=0.262$ ,  $\beta=0.275$ ,  $P<0.05$ ) and 6 months ( $\gamma=0.308$ ,  $\beta=0.336$ ,  $P<0.05$ ). However, Disease Activity Score 28–CRP (DAS) was not a predictor of  $\Delta$ TSS. [Conclusions] Our data confirm the evidence that synovial PD activity more accurately reflects active synovial inflammation (which actually causes joint destruction) than do conventional measures in RA patients treated with Bio.

### W30-4

#### Assessment of large joint destruction and FDG-PET/CT findings in patients with rheumatoid arthritis

Takahito Suto, Koichi Okamura, Yukio Yonemoto, Chisa Okura, Kenji Takagishi  
Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine, Gunma, Japan

Conflict of interest: None

[Objectives] The assessments of joint destruction in RA patients are generally restricted to the hands and feet. Few studies have been reported about large joints. <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (FDG PET) can assess the synovitis in large joints of RA. The aim of our study was to investigate the association between large joint destruction and the FDG-PET/CT findings. [Methods] In 23 RA patients (6 men and 17 women; mean age, 66.9 $\pm$ 7.9 years), FDG-PET/CT was performed at baseline and 6 months after the initiation of biologics. The patterns of FDG uptakes in large joints (shoulder, elbow, hand, hip, knee, and ankle) were analyzed using maximum standardized uptake value (SUV max). Radiographs of 276 large joints at baseline and after 2 years were assessed with Larsen's method. [Results] In 33 of 264 joints (12 artificial joints at baseline were excluded), progression of joint destruction was detected. The SUV max at baseline, at 6 months and DAS28-ESR at 6, 12, 24 months were statistically higher in the group showing progression of joint destruction. [Conclusion] The FDG uptake was higher in the large joint with progression of destruction. The lower disease activity at 6 months after the biologics is important to avoid the large joint destruction in 2 years.

### W30-5

#### Analysis of prognosis factors for functional disability in rheumatoid arthritis

Moritoshi Furu<sup>1,3</sup>, Motomu Hashimoto<sup>1</sup>, Takao Fujii<sup>1,2</sup>, Hiromu Ito<sup>1,3</sup>, Masahiro Ishikawa<sup>1,3</sup>, Noriyuki Yamakawa<sup>2</sup>, Chikashi Terao<sup>4</sup>, Wataru Yamamoto<sup>6</sup>, Hiroyuki Yoshitomi<sup>3,5</sup>, Hiroko Ogino<sup>3</sup>, Shuichi Matsuda<sup>3</sup>, Tsuneyo Mimori<sup>1,2</sup>

<sup>1</sup>Department of the Control for Rheumatic Diseases, Kyoto University

Graduate School of Medicine, Kyoto, Japan, <sup>2</sup>Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>3</sup>Department of Orthopaedic Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>4</sup>Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>5</sup>Center for Innovation in Immunoregulatory Technology and Therapeutics, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>6</sup>Kurashiki Sweet Hospital, Okayama, Japan

Conflict of interest: Yes

[Objectives] Functional disability is one of most important factor which should be improved in treatment with rheumatoid arthritis (RA). The aim of this study is to explain prognosis factors for functional disability in RA. [Methods] We chose the 301 of consecutive RA patients, with both 2012 and 2013 RA survey in our observational cohort, and assessed clinical variables including age, duration, stage, class, ACPA, RF, DAS28,  $\Delta$ DAS28 (DAS28<sup>2013</sup> minus DAS28<sup>2012</sup>), HAQ,  $\Delta$ HAQ (HAQ<sup>2013</sup> minus HAQ<sup>2012</sup>), modified Total Sharp score (mTSS), and DMARDs. We search prognosis factor for  $\Delta$ HAQ by multivariate analyses. [Results] Mean age was 62.1 years old. Mean disease duration was 14.5 years. MTX was used 71.1% of patients. Biologics was used 32.6% of patients. Mean follow-up time was 414.5 days. Prognosis factors for  $\Delta$ HAQ > 0 were no-usage of MTX (OR1.98,  $p=0.02$ ) and no-usage of biologics (OR 2.63,  $p<0.01$ ). There was no correlation between  $\Delta$ HAQ and DAS28<sup>2012</sup>. There was statistically correlation between  $\Delta$ HAQ and  $\Delta$ DAS28 ( $r=0.43$ ,  $p<0.01$ ). [Conclusion] Our study demonstrated that prognosis factors for functional disability in RA were no-usage of both MTX and biologics.

### W30-6

#### Examination to achieve low disease activity for elderly onset RA over 65 years old

Keiko Kobayashi, Norihiko Kato

Ootomi Rheumatology and Orthopedics Clinic, Shizuoka, Japan

Conflict of interest: None

[Objectives] We examine the rate of achieving low disease activity (LDA) for EORA patients in 65-74 years old (group A), 75-84 years old (group B) and over 85 years old (group C). [Methods] This is a retrospective study of 87 EORA patients in out-patient clinic. [Results] Group A contained 61 patients, group B contained 24 patients and group C contained 2 patients. MTX group contained 52 patients (59.8%) and Non-MTX group contained 35 patients (40.2%). MTX group contained 40/11/1 patient, and the average dose of MTX are 4.2/3.2/2mg. Non-MTX group contained 21/13/1 patient, and introducing of DMARD are SASP, TAC, BU, MZB, AZ, ACT and REF. Bio therapy introduce 12 patients (19.6%) and MTX group contained 11 patients (ETN for 6, TCZ for 4, GLM for 2 and ADA for 1 patient). PSL introduce 37 patients (36.7%) and the average dose of PSL are 7.3/6.1/5mg. The rate of achieving of LDA are 85%(85.2/83.3/100%). MTX group are better than Non-MTX group. The rate of achieving of LDA in MTX group contained 84.6/58.3/100%, and the rate of achieving of LDA in Non-MTX group contained 81.8/91.6/100. DAS and PSL are important role of achieving of LDA. [Conclusion] Our data suggested that it is possible to achieve of LDA for EORA patients over 65 years old to introduce DMARD, BIO and PSL even if it introduce MTX or not.

### W31-1

#### Decrease in dose of methotrexate during DAS28 remission state was a significant factor associated with early deterioration in patients with RA using the IORRA cohort

Kumi Shidara, Eisuke Inoue, Eiichi Tanaka, Rei Yamaguchi, Yoko Shimizu, Akiko Kobayashi, Daisuke Hoshi, Naoki Sugimoto, Ayako Nakajima, Shigeki Momohara, Atsuo Taniguchi, Hisashi Yamanaka  
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Objectives] To investigate risk factors for early deterioration after achieving DAS28 remission state in RA patients in daily practice.

[Methods] Among RA patients participated in the IORRA cohort between 2008 and 2009, subjects whose disease activity were in non-DAS28 remission at entry and subsequently sustained DAS28 remission for 1 year were extracted. Cox regression analyses were conducted to examine risk factors for early deterioration within 3 years after sustained 1-year DAS28 remission state. [Results] A total of 841 patients were analyzed. Proportions of the patients whose disease activity were deteriorated within 1, 2 and 3 years after sustained 1-year DAS28 remission state were 41.4%, 57.0% and 64.4%, respectively. Cox regression analyses confirmed that longer disease duration ( $p=0.045$ ), higher DAS28 score during 1-year DAS28 remission ( $p<0.0001$ ) and decrease in dose of methotrexate during DAS28 remission state ( $p=0.03$ ) were the significant factors associated with early deterioration. [Conclusion] Decrease in dose of methotrexate during DAS28 remission state was a significant factor associated with early deterioration in patients with RA in daily practice.

### W31-2

#### Smoking cessation significantly reduces failure of biologics treatment in rheumatoid arthritis: from the “NinJa” registry cohort

Takuro Nii<sup>1</sup>, Takashi Shimizu<sup>1</sup>, Akiko Yura<sup>1</sup>, Satoru Teshigawara<sup>1</sup>, Maiko Yoshimura<sup>1</sup>, Eriko Tanaka<sup>1</sup>, Yoshinori Harada<sup>1</sup>, Soichiro Tsuji<sup>1</sup>, Masato Matsushita<sup>1</sup>, Shiro Ohshima<sup>1</sup>, Jun Hashimoto<sup>1</sup>, Shigeto Tohma<sup>3</sup>, Toshihiro Matsui<sup>3</sup>, Yukihiko Saeki<sup>2</sup>

<sup>1</sup>Rheumatology, and Allergology, NHO Osaka Minami Medical Center, <sup>2</sup>Clinical Research, NHO Osaka Minami Medical Center, <sup>3</sup>Division of Rheumatology, NHO Sagami Hospital

Conflict of interest: None

[Objectives] In biologics treatment (Bio) of rheumatoid arthritis (RA), some issues remain to be resolved, including adverse effects (AE) such as serious infections, therapeutic failure (Failure) and high cost. On the other hand, smoking is thought to be one of crucial environmental factors which might affect responsiveness of anti-rheumatic drugs, including Bio. To investigate the influence of smoking on Bio-treatment in RA, we analyzed the association between the causes for discontinuation of Bio and smoking habit. [Methods] The causes of discontinuation of Bio (Failure, AE, Remission) were analyzed by using the data from the “NinJa” Registry cohort of Japanese RA patients. Smoking habit was assessed by a questionnaire and the patients were divided into three groups as smoking, non-smoking, smoking cessation. The association was analyzed statistically and shown as odds ratio (OR). [Results] In non-smoker, risk of Bio-failure was significantly reduced compared to smoker (OR 0.678;  $p=0.032$ ). The same was also observed in smoking cessation groups (OR 0.557;  $p=0.010$ ). These smoking influences were more particular in TNF inhibitors. [Conclusion] Smoking habit might affect responsiveness of Bio-treatment in RA. In addition, smoking cessation might reduce failure of Bio-treatment in RA.

### W31-3

#### Current status of RA therapy in Japanese rheumatoid arthritis patients with comorbidities in the IORRA cohort

Eiichi Tanaka, Eisuke Inoue, Rei Yamaguchi, Yoko Shimizu, Akiko Kobayashi, Naoki Sugimoto, Daisuke Hoshi, Kumi Shidara, Eri Sato, Yohei Seto, Ayako Nakajima, Shigeki Momohara, Atsuo Taniguchi, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Objectives] To assess current status of RA therapy in RA patients with comorbidities. [Methods] Among RA patients who participated in the IORRA conducted in 2013, we cross-sectionally assessed patient characteristics and treatment by comorbidities: (1) coronary artery disease [CAD], (2) cerebral disease, (3) hypertension, (4) heart failure, (5) interstitial pneumonia [IP], (6) COPD, (7) GI problem, (8) hepatic disease, (9) cancer, (10) depression, (11) diabetes, and (12) fracture. [Results] The study included 5837 patients with RA (mean age, 60.9 years; DAS28, 2.6; J-HAQ score, 0.59). The mean age was highest for CAD (71.6 years) and lowest for depression (58.1 years). The mean DAS28

was below 3.0 except for IP (3.2) and cancer (3.0), whereas all except hypertension and diabetes (0.78) had a J-HAQ score of over 0.8; in particular, fracture (1.04) and IP (1.01) were associated with disability. MTX user was lowest for IP (47.6%). Steroids user was highest for IP (68.1%). Biologics user was highest for IP (25.9%), and lowest for cancer (12.5%). [Conclusion] Although functional impairment cannot be avoided in the presence of comorbidities and the choice of RA therapy varies among different comorbidities, current RA therapy provides adequate control to achieve low disease activity.

### W31-4

#### Predicting factors of clinical outcomes in a treat-to-target implementing cohort

Fumio Hirano<sup>1,2</sup>, Waka Yokoyama<sup>1,2</sup>, Hayato Yamazaki<sup>1,2</sup>, Ryuji Koike<sup>1,2</sup>, Koichi Amano<sup>3</sup>, Yuko Kaneko<sup>4</sup>, Atsushi Kawakami<sup>5</sup>, Toshihiro Matsui<sup>6</sup>, Nobuyuki Miyasaka<sup>2</sup>, Masayoshi Harigai<sup>1,2</sup>

<sup>1</sup>Department of Pharmacovigilance, Tokyo Medical and Dental University, <sup>2</sup>Department of Rheumatology, Tokyo Medical and Dental University, <sup>3</sup>Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, <sup>4</sup>Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, <sup>5</sup>Department of Immunology and Rheumatology, Graduate School of Biomedical Science, Nagasaki University, <sup>6</sup>Department of Rheumatology, Sagami Hospital, National Hospital Organization

Conflict of interest: None

[Objective] To identify predictors of good functional and structural outcomes in a T2T implementing cohort. [Method] In the T2T Epidemiological Study, 318 RA patients with moderate to high disease activity were enrolled and treated according to T2T strategy. Of these, 201 patients enrolled by August 2012 and followed up for 48 weeks were analyzed. Predictors of HAQ remission and  $\Delta$ mTSS<smallest detectable change (SDC) at week 48 were identified using multivariate logistic regression analysis. [Results] Patient characteristics were as follows: female 77%; mean age 61; mean disease duration 57 months. At week 48, 47% achieved SDAI remission, 59% achieved HAQ remission and 76% showed  $\Delta$ mTSS<SDC. Factors [odds ratio (95%CI)] significantly associated with HAQ remission were Steinbrocker's stage 1 or 2 [3.89 (1.71-8.88),  $p<0.01$ ], baseline HAQ [0.21 (0.12-0.37),  $p<0.001$ ], no corticosteroid use [3.08 (1.48-6.41),  $p<0.01$ ] and SDAI remission at week 12 [2.87 (1.05-7.82),  $p<0.05$ ]. Factors associated with  $\Delta$ mTSS<SDC were no history of joint replacement due to RA [4.76 (1.06-21.5),  $p<0.05$ ] and SDAI remission at week 12 [5.91 (1.16-30.2),  $p<0.05$ ]. [Conclusion] To obtain good functional and structural outcomes at week 48 using T2T strategy, it is important to achieve SDAI remission at week 12.

### W31-5

#### A longitudinal study of factors contributing to the worsening of absenteeism in patients with rheumatoid arthritis based on the IORRA cohort

Eiichi Tanaka, Eisuke Inoue, Rei Yamaguchi, Yoko Shimizu, Akiko Kobayashi, Naoki Sugimoto, Daisuke Hoshi, Kumi Shidara, Eri Sato, Yohei Seto, Ayako Nakajima, Shigeki Momohara, Atsuo Taniguchi, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Objectives] To identify factors contributing to early worsening of absenteeism in Japanese patients with RA in daily practice. [Methods] The study population consisted of RA patients working for pay who participated in the IORRA in 2012 to 2013, had an absenteeism score of 0 as determined by the Work Productivity and Activity Impairment (WPAI) at baseline, and could be followed up for at least 6 months. The time to 10% or more absenteeism was tested by a Cox regression analysis to identify factors contributing to the worsening of absenteeism. [Results] The study included 1941 patients with RA (mean age, 50.6 years; females, 79.3%; DAS28, 2.6; J-HAQ, 0.32). Absenteeism first exceeded 10% at 6, 12 and 18 months in 47 (cumulative probability of worsening: 2.4% [95%CI: 1.7-3.1%]), 33 (4.5% [3.5-5.4%]) and 20 (6.2% [5.0-7.4%]) pa-

tients, respectively. Multivariate Cox regression analysis showed lower EQ-5D scores at baseline ( $p = 0.01$ ) and steroid dose at baseline ( $p = 0.01$ ) were significantly associated with earlier worsening of absenteeism. [Conclusion] Factors contributing to earlier worsening of absenteeism in RA patients were identified in daily practice. Preventing QOL deterioration without steroid use might be important in stopping the progression of work impairment.

### W31-6

#### Analysis of prognosis factors for sustained clinical remission in rheumatoid arthritis

Moritoshi Furu<sup>1,3</sup>, Motomu Hashimoto<sup>1</sup>, Takao Fujii<sup>1,2</sup>, Hiromu Ito<sup>1,3</sup>, Masahiro Ishikawa<sup>1,3</sup>, Noriyuki Yamakawa<sup>2</sup>, Chikashi Terao<sup>4</sup>, Wataru Yamamoto<sup>6</sup>, Hiroyuki Yoshitomi<sup>3,5</sup>, Hiroko Ogino<sup>3</sup>, Shuichi Matsuda<sup>3</sup>, Tsuneyo Mimori<sup>1,2</sup>

<sup>1</sup>Department of the Control for Rheumatic Diseases, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>2</sup>Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>3</sup>Department of Orthopaedic Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>4</sup>Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>5</sup>Center for Innovation in Immunoregulative Technology and Therapeutics, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>6</sup>Kurashiki Sweet Hospital, Okayama, Japan

Conflict of interest: Yes

[Objectives] The sustained clinical remission in rheumatoid arthritis (RA) may result in radiological remission. The aim of this study is to explain prognosis factors for sustained clinical remission in RA. [Methods] We chose the 301 of consecutive RA patients, with both 2012 and 2013 RA survey in our observational cohort, and assessed clinical variables. The maintain rate for clinical remission was determined, and search prognosis factor for sustained clinical remission by multivariate analyses. [Results] Mean age was 62.1 years old. Mean disease duration was 14.5 years. Mean follow-up time was 414.5 days. Mean number of visits was 8.5 times. Mean maintain rate was 30.4% for SDAI. 253 patients with more than three visits were analysed. Prognosis factors for maintain rate of SDAI were stage ( $t=-2.59$ ,  $p=0.01$ ), class ( $t=-3.25$ ,  $p<0.01$ ), PtGH ( $t=-3.26$ ,  $p<0.01$ ), and usage of biologics ( $t=-4.17$ ,  $p<0.01$ ). [Conclusion] Our study demonstrated that prognosis factors for sustained clinical remission in RA were stage, class, PtGH, and usage of biologics.

### W32-1

#### Baseline level of Procalcitonin can predict clinical remission in biologic naive rheumatoid arthritis (RA) patients treated with tocilizumab (TCZ)

Takashi Shimizu<sup>1</sup>, Soichiro Tsuji<sup>1</sup>, Takuro Nii<sup>1</sup>, Akiko Yura<sup>1</sup>, Satoru Teshigawara<sup>1</sup>, Maiko Yoshimura<sup>1</sup>, Eriko Tanaka<sup>1</sup>, Yoshinori Harada<sup>1</sup>, Masato Matsushita<sup>1</sup>, Shiro Ohshima<sup>2</sup>, Jun Hashimoto<sup>1</sup>, Yukihiko Saeki<sup>2</sup>

<sup>1</sup>Rheumatology and Allergology, NHO Osaka Minami Medical Center, Osaka, Japan, <sup>2</sup>Clinical Research, NHO Osaka Minami Medical Center, Osaka, Japan

Conflict of interest: None

[Objectives] It is reported some biomarkers predict clinical remission for patients of (RA) treated with TCZ, but their clinical usefulness have not reached consensus. It is known that Procalcitonin (PCT), a biomarker of infection, is suppressed by IFN- $\gamma$ . Serum level of IFN- $\gamma$  of RA patients is higher than that of healthy control and the relation between IFN- $\gamma$  and efficacy of Biologic agent (Bio) was recently reported. Using Baseline (BL) PCT as a surrogate biomarker of IFN- $\gamma$ , we investigated whether BL PCT can predict clinical remission after treated with TCZ. [Methods] 36 Bio naive RA patients who were measured BL PCT before administration of TCZ from July 2008 to April 2014 in our hospital were retrospectively examined. The patients were divided into 2 groups, based on Clinical remission (DAS28-ESR $<2.6$ ) and receiver operating characteristic (ROC) analysis was performed and cut-off values (COV) of BL PCT was found. [Results] BL PCT was significantly difference between the remission and non-remission groups ( $p=0.001$ ). The COV were 0.027ng/ml. The Clinical remission ratio at 52 Week of U group was significantly

higher than O group. [Conclusion] BL PCT is a useful biomarker for prediction of clinical remission in Bio naive RA patients treated with TCZ.

### W32-2

#### Glucose intolerance is a predictive factor of drug survival on biologics therapy in patients with rheumatoid arthritis

Masaaki Isono, Yuji Hirano, Shinya Hirabara

Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan

Conflict of interest: None

[Objectives] On previous study we found glucose intolerance can be a predictive factor of drug survival on biologics (BIO) therapy in patients with rheumatoid arthritis (RA). [Methods] 245 RA patients treated with any of BIO were included in this retrospective study. Switching one biological agent to another was defined as continuation of BIO therapy. Patients were divided into two groups, patients with glucose tolerance (group I) and glucose intolerance (group II). Baseline characteristics, BIO survival rate and disease activity at last follow up were compared. [Results] Baseline characteristics: We found significant difference between two groups for mean age (56.7/65.4), eGFR (92.9/77.6), PSL-concomitant rate (52.5%/83.3%), MTX-concomitant rate (85.6%/60%). We found significant difference for SDAI and mHAQ on last follow up though no significant difference were found on baseline. BIO survival rate: Significant difference were noted on survival rate ( $p=0.0003$ ). [Conclusion] Comparing the baseline group II had factors to interfere with drug survival, such as low renal function, high PSL-concomitant rate and low MTX-concomitant rate. Consequently, group II had worse BIO survival rate and disease activity. Glucose intolerance is a predictive factor of drug survival on biologics therapy.

### W32-3

#### The interval of administration of adalimumab might be extended after the achievement of low disease activity - KABUKI study -

Tadashi Okano<sup>1</sup>, Tatsuya Koike<sup>2,3</sup>, Kentaro Inui<sup>1</sup>, Masahiro Tada<sup>1</sup>, Yuko Sugioka<sup>2</sup>, Kenji Mamoto<sup>1</sup>, Makoto Wada<sup>4</sup>, Hiroaki Nakamura<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan, <sup>2</sup>Center for Senile Degenerative Disorders (CSDD), Osaka City University Medical School, Osaka, Japan, <sup>3</sup>Search Institute for Bone and Arthritis Disease (SINBAD), Wakayama, Japan, <sup>4</sup>Kyoto Yamashiro General Medical Center

Conflict of interest: None

[Objectives] Adalimumab (ADA) treatment has been established to be effective treatment for patients with rheumatoid arthritis (RA). To extend the interval of ADA administration after the achievement of low disease activity (LDA) might be important for safety and economic reasons. [Methods] Sixty-eight patients treated with ADA every other week treatment were included in this prospective randomized study (KABUKI study). Patients achieving LDA (DAS28-ESR $\leq 3.2$ ) at week 24 were randomly assigned to receive ADA 40 mg every 2 or 4 weeks from week 24 to week 48. [Results] Of 68 patients, 61 patients continued ADA 40 mg every other week until week 24. In these 61 patients, the disease activity had rapidly decreased from week 4 in 29 patients with LDA at week 24 compared with 32 patients above LDA at week 24. After week 24, the disease activity was increased in only one patient of ADA 40 mg every 4 weeks group, however others had kept LDA as well as patients receiving ADA 40 mg every other week. The increase of power Doppler signal in US assessment was not found in patients with ADA 40 mg every 4 weeks. [Conclusion] Treatment with ADA 40 mg every 4 weeks might be effective as well as ADA 40 mg every other week in patients with RA after the achievement of LDA at 24 weeks.

### W32-4

#### **Titers of Anti-CCP, anti-mutated citrullinated vimentin antibodies and rheumatoid factor in sera from rheumatoid arthritis patients treated with intravenous biological disease-modifying anti-rheumatic drugs**

Sumie Hiramatsu<sup>1</sup>, Takao Fujii<sup>2</sup>, Motomu Hashimoto<sup>2</sup>, Masahiro Ishikawa<sup>3</sup>, Moritoshi Furu<sup>2</sup>, Hiromu Ito<sup>3</sup>, Tsuneyo Mimori<sup>1,2</sup>

<sup>1</sup>Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, <sup>2</sup>Department of the Control for Rheumatic Diseases, Graduate School of Medicine, Kyoto University, <sup>3</sup>Department of Orthopedic Surgery, Graduate School of Medicine, Kyoto University

Conflict of interest: None

[Objectives] Anti-CCP antibody (Ab) titers appear not to correlate with disease activity. We examined clinical significance of anti-mutated citrullinated vimentin (MCV) Abs in addition to anti-CCP Abs and rheumatoid factor (RF) in RA patients treated with intravenous biological disease-modifying anti-rheumatic drugs (bDMARDs). [Methods] We analyzed 56 RA patients (average age= 58 years old, disease duration= 7.9 years, M:F=12:44, DAS28 = 4.19), who received infliximab (IFX, 24 patients), tocilizumab (TCZ, 13), and abatacept (ABT, 19). We examined the change of DAS28 and titers of RF, anti-CCP and MCV Abs before and 3 month after the bDMARD initiation. [Results] In our 56 patients, 41 (73%), 45 (80%), and 45 (80%) were positive for anti-CCP, MCV Abs, and RF, respectively. Although DAS28 was significantly decreased after the bDMARD initiation, anti-CCP titers did not change at 3 month. On the other hand, anti-MCV titers were significantly decreased in TCZ (403 vs. 276 U/ml,  $P=0.001$ ) and ABT (668 vs. 511 U/ml,  $P=0.020$ ) users and RF titers was decreased in IFX and TCZ users. [Conclusion] Decline of RA disease activity during the first 3 months after bDMARD initiation is associated with the decreased anti-MCV (TCZ and ABT) or RF (IFX and TCZ) titers, but not anti-CCP titers.

### W32-5

#### **The predictive factor of response to TCZ for patients with rheumatoid arthritis refractory to a TNF inhibitor: a retrospective study using the Y-CURD registry**

Yosuke Kunishita<sup>1,2</sup>, Ryusuke Yoshimi<sup>1,2</sup>, Yumiko Sugiyama<sup>1,2</sup>, Naomi Tsuchida<sup>1,2</sup>, Daiga Kishimoto<sup>1,2</sup>, Reikou Kamiyama<sup>1,2</sup>, Koji Kobayashi<sup>2,4</sup>, Toshiyuki Watanabe<sup>2,3</sup>, Rumiko Miyagi<sup>2,7</sup>, Takeaki Uehara<sup>2,10</sup>, Kaoru Minegishi<sup>1,2</sup>, Maasa Hama<sup>1,2</sup>, Yohei Kirino<sup>1,2</sup>, Yukiko Asami<sup>2,9</sup>, Tetsu Yamazaki<sup>2,5</sup>, Akiko Sekiguchi<sup>2,8</sup>, Akiko Suda<sup>2,3</sup>, Haruko Ideguchi<sup>2,7</sup>, Atsushi Ihata<sup>2,4</sup>, Shigeru Ohno<sup>2,3</sup>, Atsuhisa Ueda<sup>1,2</sup>, Mitsuhiro Takeno<sup>2</sup>, Takako Kawai<sup>2,6</sup>, Toshihisa Igarashi<sup>2,5</sup>, Shohei Nagaoka<sup>2,4</sup>, Yoshiaki Ishigatsubo<sup>1,2</sup>

<sup>1</sup>Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan, <sup>2</sup>Y-CURD Study Group, <sup>3</sup>Rheumatic Disease Center, Yokohama City University Medical Center, Yokohama, Japan, <sup>4</sup>Department of Rheumatology, Yokohama Minami Kyosai Hospital, Yokohama, Japan, <sup>5</sup>Department of Rheumatology, Yamato Municipal Hospital, Yamato, Japan, <sup>6</sup>Department of Internal Medicine, Yokohama Hodogaya Central Hospital, Yokohama, Japan, <sup>7</sup>Department of Rheumatology, National Hospital Organization Yokohama Medical Center, Yokohama, Japan, <sup>8</sup>Department of Hematology and Immunology, Fujisawa City Hospital, Fujisawa, Japan, <sup>9</sup>Department of Rheumatology, Yokosuka City Hospital, Yokosuka, Japan, <sup>10</sup>Department of Rheumatology, Chigasaki Municipal Hospital, Chigasaki, Japan

Conflict of interest: None

[Objectives] The aim of the study was to clarify predictive factors of efficacy of tocilizumab (TCZ) in patients with rheumatoid arthritis (RA) refractory to TNF inhibitors (TNFi) as the first biologics. [Methods] We retrospectively investigated clinical outcomes of RA patients who have been treated with a TNFi as the first biologic, followed by treatment with TCZ, in the Y-CURD registry, the integrated database of patients at our department and its affiliated hospitals. They were divided into groups based on EULAR response criteria and the baseline parameters were compared among the groups. [Results] Of 20 patients recruited, 12 and 8 showed good response (GR) and moderate response (MR), respectively,

to the first 3 to 6-month treatment with TCZ. Remaining 9 dropped out of the study. There were no significant differences in age, sex, rheumatoid factor, anti-cyclic citrullinated peptide antibody, drug usage, tender joint count, swollen joint count, patient's global health assessment, serum CRP, and ESR between the GR and MR groups. On the other hand, serum MMP-3 level was higher in GR group as compared to MR group ( $P = 0.05$ ). [Conclusion] Serum MMP-3 level might be a predictive factor of response to TCZ for the RA patients refractory to TNFi as the first biologics.

### W32-6

#### **Factor that can predict comprehensive disease remission in rheumatoid arthritis treatment**

Ichiro Yoshii

Yoshii Hospital from Medical Corporation Genyu

Conflict of interest: None

[Objectives] Comprehensive disease remission (CDR) is ultimate target in rheumatoid arthritis (RA) treatment. We have investigated factors for prediction of CDR. [Methods] 579 patients who had been treated more than 1 year have been analyzed in this study. We accepted clinical disease activity index (CDAI) for disease activity control index, yearly progress of Sharp/van der Heijde score (dSHS) for joint deformity speed, and modified health assessment questionnaire (mHAQ) for activity in daily life. When one index attained remission, counted as one. CDR grouping was done according to summarized points from these indices. Mean value of each of core sets for SDAI, matrix metalloproteinase3 (MMP-3) in their followed term, term length from baseline to first achieved clinical remission in DAS28, and SDAI, age at baseline, and SHS at baseline, are chosen as parameter. These values were compared for each group statistically with Mann-Whitney U test. [Results] CDR is correlated with PS for all of the two of point groups. For each component, mHAQ and CDAI correlated with PS, and dSHS correlated with MMP-3 significantly. [Conclusion] It is strongly suggested that monitoring of pain degree and MMP-3 is important to predict CDR, and to control these parameters should result in CDR.

### W33-1

#### **Serum levels of GDF-15 relate with pathogenesis in IgG4-related disease**

Shin-ya Kawashiri<sup>1,2</sup>, Tomoki Origuchi<sup>2,3</sup>, Ayako Nishino<sup>2</sup>, Shoichi Fukui<sup>2</sup>, Sosuke Tsuji<sup>2</sup>, Masataka Umeda<sup>2</sup>, Yoshiro Horai<sup>2</sup>, Yoshikazu Nakashima<sup>2</sup>, Takahisa Suzuki<sup>2</sup>, Tomohiro Koga<sup>2</sup>, Naoki Iwamoto<sup>2</sup>, Kunihiro Ichinose<sup>2</sup>, Mami Tamai<sup>2</sup>, Hideki Nakamura<sup>2</sup>, Kiyoshi Aoyagi<sup>1</sup>, Atsushi Kawakami<sup>1</sup>

<sup>1</sup>Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, <sup>2</sup>Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, <sup>3</sup>Department of Health Sciences, Nagasaki University Graduate School of Biomedical Sciences

Conflict of interest: None

[Objectives] We evaluated the association of serum GDF-15 levels and pathogenesis of IgG4-related disease (IgG4RD). [Methods] Serum levels of GDF-15 were examined by ELISA in 20 patients with IgG4RD, 12 patients with primary Sjogren's syndrome (pSS) and Castleman's disease, and 20 healthy controls. Additionally, we analyzed the relationship between organ involvements in patients with IgG4RD and serum levels of GDF-15. [Results] In IgG4RD patients, age (median) was 61 years, men: women ratio 14: 6 and serum levels of IgG4 (median) 490 mg/dl. Serum levels of GDF-15 (median) were 1537 pg/ml in IgG4RD patients. It was significantly higher than health controls (582 pg/ml,  $p = 0.01$ ) and pSS (358 pg/ml,  $p < 0.0001$ ). In IgG4RD patients with organ involvements other than lacrimal glands, salivary glands, lymph nodes, serum levels of GDF-15 but not IgG4 were significantly higher than patients with only the above involvements ( $p < 0.001$ ). [Conclusion] Serum levels of GDF-15 were high in patients with IgG4RD, and it was suggested to relate with pathogenesis in IgG4RD.



### W33-2

#### The relationship between cholinesterase, number of organ involvement and serum fibrotic markers in Japanese patients with IgG4-related disease

Kazu Ode<sup>1</sup>, Yoshinori Taniguchi<sup>1</sup>, Tatsuki Matsumoto<sup>1</sup>, Yoshiko Shimamura<sup>1</sup>, Koji Ogata<sup>1</sup>, Shuichi Nakayama<sup>1</sup>, Kosuke Inoue<sup>1</sup>, Makoto Tsugita<sup>1</sup>, Taro Horino<sup>1</sup>, Susumu Nishiyama<sup>2</sup>, Yasuhiko Yoshinaga<sup>2</sup>, Mitsuhiro Kawano<sup>3</sup>, Yoshio Terada<sup>1</sup>

<sup>1</sup>Department of Endocrinology, Metabolism, Nephrology and Rheumatology, Kochi Medical School, Kochi University, <sup>2</sup>Rheumatic Disease Center, Kurashiki Medical Center, <sup>3</sup>Division of Cardiovascular Medicine, Kanazawa University Graduate School of Medical Science

Conflict of interest: None

**[Objective]** To evaluate the relationship between ChE, number of organ involvement and serum fibrotic markers in Japanese patients with IgG4-RD. **[Methods]** The clinical symptoms, laboratory, pathological and FDG-PET/CT findings of Japanese patients with IgG4-RD (n=20) were assessed. Several laboratory data of IgG4-RD with multiple organs' involvements (IRDMOI) (n=10), IgG4-RD with limited organ's involvement (IRDLOI) (n=10), AAV (n=10) and SjS (n=10) were comparatively examined. We studied the relationship between the numbers of organ involvement (NOI) and several fibrotic markers in IgG4-RD group. **[Results]** Serum ChE levels were significantly lower in IRDMOI group than IRDLOI, AAV and SjS groups. Serum Alb and IgG levels were significantly lower and CRP levels were significantly higher in AAV group. There were no significant differences in these levels between IRDMOI and SjS. In total IgG4-RD cases, ChE levels inversely correlated with NOI and fibrotic score, and fibrotic score positively correlated with NOI. Dkk-1 levels in IRDMOI were significantly lower than IRDLOI. **[Conclusion]** There were significant correlation between NOI and fibrotic markers levels in IgG4-RD, and therefore, the increase of NOI might cause more progressive fibrosis. Serum ChE could predict these phenomena.

### W33-3

#### Occurrence of glucocorticoid-induced avascular necrosis of the femoral heads in IgG4-related disease and the roles of interferon $\alpha$ to the pathogenesis

Motohisa Yamamoto<sup>1</sup>, Hidetaka Yajima<sup>1</sup>, Yui Shimizu<sup>1</sup>, Chisako Suzuki<sup>1</sup>, Yasuyoshi Naishiro<sup>1</sup>, Shunichiro Okazaki<sup>2</sup>, Satoshi Nagoya<sup>2</sup>, Hiroki Takahashi<sup>1</sup>, Kohzoh Imai<sup>3</sup>, Yasuhisa Shinomura<sup>1</sup>

<sup>1</sup>Department of Gastroenterology, Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine, Sapporo, Japan, <sup>2</sup>Department of Musculoskeletal Biomechanics and Surgical Development, Sapporo Medical University School of Medicine, Sapporo, Japan, <sup>3</sup>The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

Conflict of interest: None

**[Objectives]** We often experience the occurrence of glucocorticoid-induced avascular necrosis of femoral heads (G-AVN) in the patients with IgG4-related disease (IgG4-RD). It is known that interferon (IFN)  $\alpha$  plays a role in both pathogenesis of systemic lupus erythematosus (SLE) and G-AVN. We aimed to clarify the incidence of G-AVN in IgG4-RD and to analyze the role of IFN $\alpha$  in IgG4-RD. **[Methods]** The subjects were the 144 rheumatic patients (including 25 patients with IgG4-RD), who were treated with high dose administration of glucocorticoid (initial doses of prednisolone >35 mg/day), and were evaluated G-AVN by magnetic resonance imaging at the three months after initiation of the treatment. We evaluated the incidence of G-AVN in IgG4-RD. We histopathologically analyzed the IFN $\alpha$ /TLR7/9 immunostaining for the salivary gland specimens of IgG4-RD to disclose the roles of innate immunity to G-AVN. **[Results]** G-AVN was observed in 55 cases. The incidence of G-AVN in SLE and IgG4-RD were 61.0% and 28.0%, respectively. The germinal centers in the specimens from IgG4-RD were strongly stained by IFN $\alpha$  and TLR7. **[Conclusion]** The incidence of G-AVN in IgG4-RD was very high as well as that in SLE. It is considered that IFN $\alpha$  and its inducing signals also play a role in the occurrence of G-AVN.

### W33-4

#### Appearance of new organ involvement in clinical course of IgG4-related disease

Ichiro Mizushima<sup>1</sup>, Shunsuke Tsuge<sup>1</sup>, Kazunori Yamada<sup>2</sup>, Takeshi Zoshima<sup>2</sup>, Kiyoaki Ito<sup>2</sup>, Akikatsu Nakashima<sup>1</sup>, Mitsuhiro Kawano<sup>2</sup>

<sup>1</sup>Division of Nephrology and Rheumatology, Department of Internal Medicine, Ishikawa Prefectural Central Hospital, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Kanazawa University Hospital

Conflict of interest: None

**[Objectives]** Organ involvement metachronously and multiply appears in IgG4-related disease (IgG4-RD). However, the frequency of appearance of new organ involvement (NOI) and the factors related to it have not been elucidated. This study was conducted to evaluate these points. **[Methods]** We retrospectively evaluated the frequency of appearance of NOI during the clinical course and the factors related to it in 76 patients with IgG4-RD. **[Results]** The patients were 47 men and 29 women with an average age of 64.6 years. An average serum IgG4 level was 672 mg/dL, and an average number of involved organs was 2.7. After the diagnosis, 57 patients (Group A) received maintenance corticosteroid (CS) therapy after initial CS therapy, 2 (Group B) stopped CS therapy after it, and the other 17 (Group C) were observed without CS therapy. During a mean follow-up period of 35.8 months, appearance of NOI was observed in 7 patients (9.2%), who included 2 of Group A, 2 of Group B, and 3 of Group C. Compared with Group B and C, Group A showed significantly younger age (62.9 vs 69.4,  $P=0.016$ ), more involved organs at the diagnosis (2.96 vs 1.95,  $P=0.002$ ), and lower frequency of appearance of NOI (3.5% vs 26.3%,  $P=0.009$ ). **[Conclusion]** Our data suggests that maintenance CS therapy may prevent appearance of NOI.

### W33-5

#### The long-term renal outcome of glucocorticoid therapy in patients with IgG4-related kidney

Takako Saeki<sup>1</sup>, Mitsuhiro Kawano<sup>2</sup>, Ichiro Mizushima<sup>2</sup>, Motohisa Yamamoto<sup>3</sup>, Yoshifumi Ubara<sup>4</sup>, Hitoshi Nakashima<sup>5</sup>, Yoko Wada<sup>6</sup>, Tomoyuki Ito<sup>1</sup>, Hajime Yamazaki<sup>1</sup>, Ichiei Narita<sup>6</sup>, Takao Saito<sup>7</sup>

<sup>1</sup>Department of Internal Medicine, Nagaoka Red Cross Hospital, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Kanazawa University Hospital, <sup>3</sup>First Department of Internal Medicine, Sapporo Medical University School of Medicine, <sup>4</sup>Nephrology Center, Toranomon Hospital, <sup>5</sup>Division of Nephrology and Rheumatology, Department of Internal Medicine, Faculty of Medicine, Fukuoka University, <sup>6</sup>Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, <sup>7</sup>General Medical Research Center, Faculty of Medicine, Fukuoka University

Conflict of interest: None

**[Objectives]** To examine the long-term renal outcome of glucocorticoid (GC) therapy in patients with IgG4-related kidney disease (IgG4-RKD). **[Methods]** This retrospective multi-center cohort study included 44 patients with definite IgG4-RKD in whom the eGFR before GC therapy had been less than 60 ml/min. We examined renal function at the last review in patients who had been followed up for over 36 months. **[Results]** Thirty-one of the 44 patients were enrolled. The follow-up period after therapy was 37 – 210 months (mean 72.4 and median 56). Twenty-nine of the 31 patients were maintained with low-dose GC (mean prednisolone dose 4.6 mg daily). No patient showed progression to end-stage renal disease. There was no significant difference between eGFR at 1 month after treatment (44.5  $\pm$ 12.8) and eGFR at the last review (43.5  $\pm$ 11.3 ml/min). **[Conclusion]** In IgG4-RKD, development of end-stage renal disease is extremely rare and recovery of renal function during the first month of this treatment can be maintained for a long period on low-dose GC maintenance therapy.

### W33-6

#### Usefulness of FDG-PET imaging and serological biomarkers in Lymphadenopathy of IgG4-related disease

Hiroki Ozaki, Risa Wakiya, Hiromi Shimada, Shusaku Nakashima, Yohei Takeuchi, Miharuru Izumikawa, Tomohiro Kameda, Kentaro Susaki, Hiroaki Dobashi

Department of Internal Medicine, Division of Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University, Kagawa, Japan

Conflict of interest: None

(Objectives) Lymphadenopathy is a common occurrence in IgG4-RD, but it is necessary to distinguish malignancy, infectious disease and connective tissue disease. In this study, we investigated the utility of FDG-PET and serological biomarkers to determine the diagnosis who suspected of having IgG4-RD. (Methods) We studied 27 cases with suspected IgG4-RD in our facility between Jan. 2008 and Dec. 2014. The diagnosis for IgG4-RD was based on comprehensive diagnostic criteria for IgG4-RD. We retrospectively studied the relation of serum IgG4 levels, sIL2-R and maximum standardized uptake value (SUVmax) of FDG-PET. (Results) Lymphadenopathy were detected in 20 of 27 cases (IgG4-RD definite: 8, IgG4-RD possible: 5, IgG4-RD probable: 1, infectious disease: 2, SLE: 1, EGPA: 1, malignant lymphoma: 1, Castleman disease: 1). In IgG4-RD serum IgG4 level were significantly high and sIL-2R were relatively low value in comparison with other diseases. The difference did not accept it in SUVmax. (Conclusions) In this study, we examined cases with lymphadenopathy. It was difficult to distinguish other diseases from IgG4-RD using SUVmax. It was suggested that the possibility we could distinguish the disease by combined serum IgG4 levels and sIL-2R.

### W34-1

#### A retrospective study of 51 patients with spondyloarthritis

Sho Sendo, Yuiko Kamei, Daisuke Waki, Ikuko Naka, Kousaku Tsuda, Takaichi Okano, Kengo Akashi, Miwa Nishida, Keisuke Nishimura, Soshi Takahashi, Yo Ueda, Akira Onishi, Yoshinori Kogata, Goichi Kageyama, Jun Saegusa, Akio Morinobu  
Department of Rheumatology and Clinical Immunology, Kobe University Graduate School of Medicine, Hyogo, Japan

Conflict of interest: None

[Objective] To evaluate the clinical characteristics of spondyloarthritis (SpA). [Method] We retrospectively analyzed the clinical characteristics of 51 patients with SpA in Kobe University Hospital. [Results] We identified 51 patients with SpA (27 men, 24 women), including 8 AS, 25 PsA, 9 PAO (palmoplantar pustulotic arthro-osteitis), 3 IBD-SpA, 2 ReA and 6 uSpA (undifferentiated). Thirty eight patients (75%) fulfilled the ASAS classification criteria for axial or peripheral SpA. HLA-B27 was measured in 14 cases and was positive in 4 cases. The mean age (year-old) was 53.3±13.4 (from 23 to 79) (AS:62.0, PsA:49.2, PAO:60.8, IBD-SpA:46.0, ReA:59.0, uSpA:45.6). The median time (years) from the onset to diagnosis was as follows; AS:17, PsA:2.5, PAO:2 IBD-SpA:0.9, ReA:1.1 and uSpA:1.5. Serum CRP level (mg/dl) at the time of diagnosis was as follows; AS:1.24, PsA:0.8, PAO:0.9, IBD-SpA:4.1, ReA:8.3, uSpA:1.3. Corticosteroid was used in 27 cases (52.9%), DMARDs in 34 (66.7%), NSAIDs in 36 (70.6%) and TNF  $\alpha$  inhibitor in 15 (29.4%). [conclusion] The patients with AS needed to be diagnosed for a long time from the onset. Serum CRP levels at the time of diagnosis tended to be high in the patients with IBD-SpA and ReA. Furthermore, we would evaluate the some clinical features of our SpA patients.

### W34-2

#### The analysis of four patients with ankylosing spondylitis who need switching TNF inhibitor

Kurisu Tada<sup>1</sup>, Eri Hayashi<sup>1</sup>, Michihiro Ogasawara<sup>1</sup>, Ken Yamaji<sup>1</sup>, Naoto Tamura<sup>1</sup>, Shigeto Kobayashi<sup>2</sup>, Hisashi Inoue<sup>3</sup>, Yoshinari Takasaki<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan, <sup>2</sup>Department of General Medicine, Juntendo University Koshigaya Hospital, <sup>3</sup>Department of Orthopaedic Surgery, Juntendo University School of Medicine

Conflict of interest: None

Here we show the four cases of ankylosing spondylitis who need switching TNF inhibitor. Case 1; 40 year-old man with total spine ankylosis was refractory to conventional therapy. In Jul. 2012, he was admin-

istred infliximab (IFX) and improved. In Nov. he was operated spinal shortening, but after operation he must stop IFX because of sepsis. From 2014, he started adalimumab (ADA) and improved with no infection. Case 2; 35 year-old man started IFX in 2006 and it was effective. But the efficacy was gradually weakened and he switch to ADA. Case 3; 30 year-old woman. She appeared back pain at the age of 23, and was already ankylosis in her cervical spine and sacroiliac joint. In June 2010, she administered IFX in June 2010, but her infusion interval was prolonged to 10-12 weeks because of her economical reason,. Finally she stoped IFX because of skin eruption, and she switch to ADA. Case 4; 46 year-old man was received IFX (3mg/kg) in 2008 and effective initially. But this effectiveness decrease after 2 month later and not improved even when the dose of IFX increase (5mg/kg). In Nov 2011 he switched to ADA and improved immediately. In this four swithcers with various reasons, three patients were achieved BASDAI 50 response. This efficacy was high compared with TNF naïve cases.

### W34-3

#### Current status of the treatment for Spondyloarthritis in our facility

Shohei Kawakami<sup>1</sup>, Tomohiro Kameda<sup>2</sup>, Atsushi Kondo<sup>1</sup>, Risa Wakiya<sup>2</sup>, Hiroki Ozaki<sup>2</sup>, Hiromi Shimada<sup>2</sup>, Shusaku Nakashima<sup>2</sup>, Yohei Takeuchi<sup>2</sup>, Miharu Izumikawa<sup>2</sup>, Kentaro Susaki<sup>2</sup>, Hiroaki Dobashi<sup>2</sup>

<sup>1</sup>Postgraduate Clinical Education Center, Kagawa University Hospital, Kagawa, Japan, <sup>2</sup>Department of Internal Medicine, Division of Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University, Kagawa, Japan

Conflict of interest: None

[Objectives] Treatment of rheumatoid arthritis (RA) has been progressed by biologics recently. In addition, tumor necrosis factor (TNF) inhibitor such as adalimumab (ADA) and Infliximab (IFX) has adaptation for Spondyloarthritis (SpA) including psoriatic arthritis (PSA) and ankylosing spondylitis (AS) other than RA in Japan. However, we have not enough experience of TNF inhibitor for SpA in comparison with Europe. We accumulate the treatment for SpA and examine the effectiveness for SpA treatment. [Methods] We investigated the treatment regimen and the effectiveness for SpA patients in our facility in period from August 2009 to August 2014. [Results] We treated 28 SpA patients with TNF inhibitor. TNF inhibitor treatment was continued 18 in 20 PSA cases for one year. Additionally, 17 in 18 PSA cases attained low disease activity or remission. Most of SpA patients were treated with IFX. In adverse event, we have one case of pyogenic arthritis by non-tuberculous mycobacterial infection. 6 AS patients have no severe AE. We have one effect attenuation case for IFX treatment. On the other hand, one case with ADA treatment was able to discontinue the biologics. [Conclusion] We suggest that TNF inhibitor treatment is effective for SpA. However, we have to be careful for AEs such as infection.

### W34-4

#### Two cases of palmoplantar pustulosis arthro-ostitis who developed peripheral arthritis

Jin Ikenaga<sup>1</sup>, Masataka Umeda<sup>1</sup>, Sosuke Tsuji<sup>1</sup>, Shoichi Fukui<sup>1</sup>, Ayako Nishino<sup>1</sup>, Yoshikazu Nakashima<sup>1</sup>, Takahisa Suzuki<sup>1</sup>, Yoshiro Horai<sup>1</sup>, Yasuko Hirai<sup>1</sup>, Tomohiro Koga<sup>1</sup>, Shin-ya Kawashiri<sup>1</sup>, Naoki Iwamoto<sup>1</sup>, Kunihiro Ichinose<sup>1</sup>, Mami Tamai<sup>1</sup>, Hideki Nakamura<sup>1</sup>, Tomoki Origuchi<sup>2</sup>, Atsushi Kawakami<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Unit of Translational Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan, <sup>2</sup>Department of Rehabilitation Sciences, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan

Conflict of interest: None

[Case 1] A 63-years-old woman had suffered from pain and swollen in finger joints and both wrists for one and a half years. Ultrasound examination showed active synovitis in finger joints mimicking seronegative rheumatoid arthritis (SNRA). Bone scintigraphy showed increased accumulation in the sternoclavicular joints. MRI showed active synovitis in the same sites. Based on coexisting palmoplantar pustulosis, she was diagnosed with palmoplantar pustulosis arthro-ostitis (PAO). [Case 2] A 63-years-old woman had suffered from pain and swollen of both ankles,

right knee and left wrist for two months. Ultrasound examination showed synovial thickening in finger joints, active synovitis in left wrist and huge synovial fluid in right knee mimicking SNRA. Bone scintigraphy showed increased accumulation in the sternoclavicular joints and spine. Hypertrophic osteitis of the same site also existed. Based on coexisting palmo-plantar pustulosis, she was diagnosed with PAO. The arthropathy of PAO commonly involves the sternoclavicular joints and spine. In addition, complication with peripheral arthritis has also been reported. Here we show two cases of PAO patients who were difficult in distinguishing with SNRA because the peripheral arthritis had mainly appeared at time of first visit.

### W34-5

**The effectiveness of bone scintigraphy for assessing SAPHO syndrome**  
Tomoko Kawabata<sup>1</sup>, Ken-ei Sada<sup>2</sup>, Haruki Watanabe<sup>2</sup>, Eri Katsuyama<sup>2</sup>, Takayuki Katsuyama<sup>2</sup>, Noriko Toyota Tatebe<sup>2</sup>, Koichi Sugiyama<sup>2</sup>, Katsue Sunahori Watanabe<sup>2</sup>, Hiroshi Wakabayashi<sup>2</sup>, Jun Wada<sup>2</sup>, Hirofumi Makino<sup>3</sup>

<sup>1</sup>Department of Primary Care and Medical Education, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, <sup>2</sup>Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine Dentistry and Pharmaceutical Sciences, Okayama, Japan, <sup>3</sup>Okayama University Hospital

Conflict of interest: None

**[Objectives and Methods]** We investigated the effectiveness of bone scintigraphy for assessing SAPHO syndrome at the time of diagnosis in comparison with the clinical features in 13 Japanese patients (female: 10, male: 3) diagnosed between 2005 and 2014. **[Results]** The average age at diagnosis was 52 y.o. (29-65). Three patients had arthritis before the skin lesions appeared and 10 patients developed skin symptoms in prior to the onset of arthritis. The mean CRP level was 13 g/L (0.7-52). The symptomatic lesions leading to a diagnosis were in the sternoclavicular and sternocostal joints in five cases, shoulder joints in five cases, lower back in six cases and femoral area in two cases. In contrast, on bone scintigraphy, an increased uptake in the lesions was observed in the anterior chest wall (ACW) in 92.3% of the patients, the femoral and tibial bone in 15.3%, the knee and wrist in 23.1%, the sacroiliac joint in 23.1% and the thoracic spine in 7.6%. **[Conclusions]** The affected region revealed by bone scintigraphy is wider than the area associated with clinical symptoms in patients with SAPHO syndrome. Bone scintigraphy is a useful tool for evaluating disease activity and therapeutic efficacy.

### W34-6

**TNF- $\alpha$  inhibitor therapy for SAPHO syndrome at our hospital**

Atsuma Nishiwaki<sup>1</sup>, Hitomi Haraoka<sup>1</sup>, Isamu Yokoe<sup>2</sup>, Yosuke Nagasawa<sup>1</sup>, Kaita Sugiyama<sup>1</sup>, Natsumi Ikumi<sup>1</sup>, Takamasa Nozaki<sup>1</sup>, Hirotake Inomata<sup>1</sup>, Hidetaka Shiraiwa<sup>1</sup>, Noboru Kitamura<sup>1</sup>, Yoshihiro Matsukawa<sup>1</sup>, Masami Takei<sup>1</sup>

<sup>1</sup>Nihon University School of Medicine, Tokyo, Japan, <sup>2</sup>Itabashi Chuo Medical Center, Tokyo, Japan

Conflict of interest: None

**[Objective]** We examined the efficacy of TNF- $\alpha$  inhibitor therapy for SAPHO syndrome. **[Methods]** Among 10 patients with SAPHO syndrome (5 men and 5 women) treated at Itabashi Chuo Medical Center from 2008 to 2014, 4 refractory patients received TNF- $\alpha$  inhibitors. We evaluated the pain score and physical function, with dose reduction of analgesics and anti-inflammatory drugs judged to indicate the effectiveness of the therapy. **[Results]** All 10 patients received MTX, but MTX monotherapy was only effective for pain in 3. The TNF inhibitor infliximab was given to 3 patients and etanercept was used in 1 patient. One patient receiving infliximab was switched to golimumab due to a poor response. TNF- $\alpha$  inhibitor therapy was given to patients with severe tenderness and swelling of sternocostal clavicle despite MTX, and it achieved marked improvement. Three patients had pustular dermatitis and all 3 improved on TNF- $\alpha$  inhibitor therapy. Two had concomitant spondylitis and lumbar pain improved in both; 1 patient had bamboo spine and the bone changes did not respond. TNF- $\alpha$  inhibitor therapy showed an early analgesic effect in all 4 patients that continued for a mean of 2 years. **[Conclusions]**

TNF- $\alpha$  inhibitor therapy may be an option for refractory SAPHO syndrome as well as ankylosing spondylitis.

### W35-1

**Pitfalls in diagnosis of polymyalgia rheumatica**

Akira Nishino<sup>1,2</sup>, Yohei Seto<sup>1,2</sup>, Hisashi Yamanaka<sup>2</sup>

<sup>1</sup>Tokyo Women's Medical University Yachiyo Medical Center, <sup>2</sup>Institute of Rheumatology Tokyo Women's Medical University

Conflict of interest: None

**[Background]** Since no specific diagnostic criterion for polymyalgia rheumatica (PMR) and administration of systemic glucocorticoids often dramatically improve patients' symptom even in other musculoskeletal conditions. **[Cases]** We presents three cases of different conditions initially diagnosed as PMR. Careful history taking and imaging were helpful to establish different diagnosis such as seronegative rheumatoid arthritis, psoriatic arthritis and crystal deposition disease. **[Conclusion]** There happen to be pitfalls to rely on classification criteria in diagnosis of patients with inflammatory large joint pain and elevated C-reactive proteins. It is mandatory to carefully observe through the clinical course.

### W35-2

**Sequential Ultrasonographic Observation of Twenty Cases with Polymyalgia Rheumatica**

Atsumu Osada<sup>1</sup>, Koji Kobayashi<sup>1</sup>, Atsushi Ihata<sup>2</sup>, Shohei Nagaoka<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Yokohama Minami Kyosai Hospital. Yokohama, Japan, <sup>2</sup>Department of Rheumatology and Infectious Disease, Yokohama Minami Kyosai Hospital. Yokohama, Japan

Conflict of interest: None

**PURPOSE:** To evaluate the efficacy of ultrasonography in follow-up in treatment with polymyalgia rheumatica (PMR). **METHODS:** Twenty patients, who underwent US before and at least once after administration of PSL, were enrolled. Visual analogue scale (VAS) for shoulder pain, erythrocyte sedimentation rate and C-reactive protein, and physical findings were evaluated. **RESULTS:** The average age was 76.5 years old. Eighteen patients fulfilled EULAR/ACR 2012 provisional classification criteria for PMR. The average dose of PSL was 16.6 $\pm$ 9.2mg, and average interval between administration and second US was 116 $\pm$ 139 days. US inflammatory findings were observed in three patients among eight cases who had VAS less than 1.0cm, CRP lower than 0.45mg/dl, and no physical findings. US findings improved than previous examination even in one of two case of clinical relapse. **CONCLUSIONS:** It was suggested that there is discrepancy between US findings and other clinical signs in patient under treatment with PMR.

### W35-3

**Predicting factors for cancellation of glucocorticoid therapy within two years in patients with polymyalgia rheumatica**

Takahide Ikeda<sup>1</sup>, Mikako Kawashima<sup>1</sup>, Ichiro Mori<sup>1</sup>, Hiroyuki Morita<sup>1</sup>, Tatsuo Ishizuka<sup>2</sup>

<sup>1</sup>Department of General Internal Medicine, Gifu University Graduate School of Medicine, <sup>2</sup>Center of General Internal Medicine and Rheumatology, Gifu Municipal Hospital, Gifu, Japan

Conflict of interest: None

**[Objectives]** We have examined retrospective analyses of patient characteristics and chemical examinations to clarify predicting factors, which are suggestive of the withdrawal of glucocorticoid therapy in patients with PMR. **[Methods]** A total of 39 patients with PMR diagnosed by the Birds criteria between April 2004 and March 2012 were retrospectively analyzed. A multivariate logistic regression analysis was performed using sex, age, body mass index, smoking/alcohol habits, body temperature, Birds criteria items, items of provisional criteria of the EULAR and ACR, initial dose of glucocorticoids, duration of treatment with the initial dose and patient's biochemical data as independent variables, and withdrawal of glucocorticoids as a dependent one. **[Results]** Average age of the patients was 74  $\pm$  6 years and 25 patients (64%) were men. Number

(percentage) of patients allowed to cancel glucocorticoid treatment was 18 (46%). An independent predicting factor for withdrawal of glucocorticoids within two years was the initial dose of glucocorticoids (odds ratio: 1.27). [Conclusion] Based on our observation, the minimum dose of glucocorticoid treatment should be started in patients with PMR to possibly allow withdrawal of the glucocorticoid treatment.

### W35-5

#### Cardiac involvement of relapsing polychondritis in Japan; an epidemiological study

Noboru Suzuki<sup>1</sup>, Jun Shimizu<sup>1</sup>, Hiroshi Oka<sup>2</sup>, Yoshihisa Yamano<sup>1</sup>, Kazuo Yudoh<sup>1</sup>

<sup>1</sup>St. Marianna University School of Medicine, Kawasaki, Japan, <sup>2</sup>Tokyo Medical University Hachioji Medical Center

Conflict of interest: None

[Objectives] Cardiac involvement of relapsing polychondritis (RP) was potentially lethal mainly through the valvular disorders. The aim of this study is to assess clinical characteristics of RP cardiac involvement in Japan. [Methods] A multi-institutional survey was conducted in 2009 and 2014. We conducted second survey of 16 facilities in October 2014. [Results] The average age at onset of RP patients with cardiac involvement was 62.2 years and the male to female ratio was 3.5: 1. Myocardial infarction (MI, 3 cases), angina (2 cases), heart failure (1 case), aortic aneurysm/aortitis (3 cases), aortic/mitral valve regurgitation (AR/MR, 4 cases) were recognized in the patients. We received 5 clinical data (2 MI, 2 angina, and 1 AR) of RP cardiac involvement in the second survey. All 5 patients had auricular chondritis and one patients showed bronchial involvement. All patients showed systemic inflammation, such as scleritis (2 cases), orbital cellulitis (1 case), aseptic meningitis (1 case), and encephalitis (1 case). 1 cardiac attack patient died of the MI and 1 RP patients with angina died of uncertain cause. [Conclusion] It is suggested that RP cardiac involvement was a major determinant of disease severity in Japan.

### W35-6

#### Tocilizumab for the treatment of refractory tracheobronchitis in relapsing polychondritis

Hiroshi Ito<sup>1</sup>, Hidehiro Yamada<sup>1</sup>, Shoshi Shinagawa<sup>1</sup>, Hidenori Mikage<sup>1</sup>, Hiromi Matsushita<sup>1</sup>, Machiko Mizushima<sup>1</sup>, Yoshiaki Yamasaki<sup>1</sup>, Shoichi Ozaki<sup>1</sup>, Kazuo Yudoh<sup>2</sup>, Yoshihisa Yamano<sup>2</sup>

<sup>1</sup>Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan, <sup>2</sup>Institute of Medical Science, St. Marianna University School of Medicine, Kawasaki, Japan

Conflict of interest: None

A 14-year-old female presented with costochondral pain and thickenings of the laryngotracheal walls in May 2013. Tracheotomy and biopsy resulted in the diagnosis of relapsing polychondritis. Treatment with prednisolone (60 mg/day), cyclosporine and MTX plus infliximab (3 mg/kg) all failed to taper steroid dose to stabilize tracheobronchitis. But when prednisolone was reduced, CRP became elevated and worsening of symptoms was observed. CT scan revealed severe airway narrowing and bronchial wall thickening irrespective of three injections of infliximab. Treatment with tocilizumab 8 mg/kg every two weeks was introduced in May 2014. Five months later, respiratory symptoms, airway narrowing and bronchial wall thickening improved, resulting in the reduction of prednisolone from 25 mg to 5 mg/day. Conclusion: Tocilizumab seemed effective for refractory tracheobronchitis of RP.

### W36-1

#### RF at 24 weeks of the RA patients who administrated ABT can be prediction of effectiveness at 52 weeks

Tomonori Kobayakawa<sup>1</sup>, Nobunori Takahashi<sup>1</sup>, Atsushi Kaneko<sup>2</sup>, Daihei Kida<sup>2</sup>, Masatoshi Hayashi<sup>3</sup>, Yuji Hirano<sup>4</sup>, Yasuhide Kanayama<sup>5</sup>, Koji Funahashi<sup>1</sup>, Shuji Asai<sup>1</sup>, Nobuyuki Asai<sup>1</sup>, Toki Takemoto<sup>1</sup>, Kenya Terabe<sup>1</sup>, Yutaka Yoshioka<sup>1</sup>, Toshihisa Kojima<sup>1</sup>, Naoki Ishiguro<sup>1</sup>

<sup>1</sup>Nagoya Graduate School of Medicine, <sup>2</sup>Nagoya Medical Center, <sup>3</sup>Naga-

no Red Cross Hospital, <sup>4</sup>Toyohashi Municipal Hospital, <sup>5</sup>Toyota Kosei Hospital

Conflict of interest: Yes

[Objectives] RF which applied to 2010 ACR/EULAR criteria is one of the important factor of the RA treatment. We investigated that relation of RF and ABT with RA patients. [Methods] We investigated 275 RA patients who was administrated ABT in TBCR from 2010 to 2014. We divided 275 patient four groups of the less than RF 45 IU/ml (Low) and greater than 45 IU/ml (High) at 0 week and 24 weeks. The Low-Low (LL) group was 90 patients, Low-High (LH) group was 6 patients, High-Low (HL) group was 31 patients, High-High (HH) group was 148 patients. We investigated the background and reactivity of ABT at 52 weeks. [Results] The average of age, RA duration, DAS28CRP in LL group was 67.3 years old, 11.9 years, 3.9, LH group was 67.0 years old, 15.7 years, 3.8, HL group was 61.9 years old, 7.9 years old, 4.5, and HH group was 66.4 years old, 15.9 years, 4.6. DAS28CRP of 52 weeks was 2.8 in LL group, 3.9 in LH group, 2.8 in HL group, 3.3 in HH group. Even if patients whose RF was less than 45 IU/ml at 0 weeks, RF was greater than 45 IU/ml at 24 weeks, the Effectiveness of ABT might fade off. The other hand, if patients whose RF was greater than 45 IU/ml at 0 weeks, RF was lower than 45 IU/ml at 24 weeks, ABT might effectiveness. [Conclusion] We thought that RF at 24 weeks was might be predictor of ABT.

### W36-2

#### Clinical effectiveness of abatacept in switching from tumor necrosis factor inhibitors with low dose or without methotrexate in rheumatoid arthritis patients; result from multicenter observational cohort study (Tsurumi Biologics Communication Registry; TBCR) in Japan

Toshihisa Kojima<sup>1</sup>, Nobunori Takahashi<sup>1</sup>, Atsushi Kaneko<sup>2</sup>, Daihei Kida<sup>2</sup>, Yuji Hirano<sup>3</sup>, Takayoshi Fujibayashi<sup>4</sup>, Yuichiro Yabe<sup>5</sup>, Hideki Takagi<sup>6</sup>, Takeshi Oguchi<sup>7</sup>, Masahiro Hanabayashi<sup>8</sup>, Takefumi Kato<sup>9</sup>, Tsuyoshi Watanabe<sup>10</sup>, Masatoshi Hayashi<sup>11</sup>, Yasuhide Kanayama<sup>12</sup>, Tomone Shioura<sup>13</sup>, Naoki Ishiguro<sup>1</sup>

<sup>1</sup>Orthopedic Surgery, Nagoya University Hospital, Nagoya, Japan, <sup>2</sup>Orthopedic Surgery, Nagoya, Medical Center, Nagoya, Japan, <sup>3</sup>Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan, <sup>4</sup>Orthopedic Surgery, Konan Kosei Hospital, Konan, Japan, <sup>5</sup>Rheumatology, JCHO Tokyo-Shinjyuku Medical Center, Tokyo, Japan, <sup>6</sup>Orthopedic Surgery, Nagoya Central Hospital, <sup>7</sup>Orthopedic Surgery, Anjo Kosei Hospital, Anjo, Japan, <sup>8</sup>Orthopedic Surgery, Ichinomiya Municipal Hospital, Ichinomiya, Japan, <sup>9</sup>Kato Orthopedic Clinic, Okazaki, Japan, <sup>10</sup>Orthopedic Surgery, Kariya-Toyota General Hospital, Kariya, Japan, <sup>11</sup>Rheumatology, Nagano Red Cross Hospital, Nagano, Japan, <sup>12</sup>Orthopedic Surgery, Toyota Kosei Hospital, Toyota, Japan, <sup>13</sup>Orthopedic Surgery, Shizuoka Kosei Hospital, Shizuoka, Japan

Conflict of interest: Yes

[Objectives] The purpose of this study was to identify the effectiveness of abatacept (ABT) in switching from Tumor necrosis factor inhibitor (TNFi) with low dose or without MTX in patients with RA using the multicenter registry. [Methods] A total of 69 patients who received ABT in switching from TNFi were selected. The effectiveness of ABT was explored by reason for discontinuation of previous TNFi. Predictive factors at baseline for LDA or remission (DAS28-CRP  $\leq$  3.2) at 52 weeks were identified by logistic regression analysis. [Results] The patients had significant improvement in DAS28-CRP from 4.97 at baseline to 3.56 at 52 weeks. 40% of the patients achieved LDA or remission. Patients with intolerance also had comparable improvement. Multivariate analysis showed that previous ETN was a significant [OR 0.06: 95% CI 0.01-0.74] and previous ADA was a marginal [OR 0.09: 95% CI 0.01-1.16] predictive factor for LDA or remission, compared to previous IFX. Earlier disease stage was a also significant factor [OR: 6.21 (95% CI 1.42-27.1)]. [Conclusion] Switching from TNFi to ABT with low dose or without MTX is a useful option, especially for patients with earlier disease stage. Previous use of TNFi could be important information to predict good outcome under this condition.

### W36-3

#### Three year retention rate of abatacept therapy for patients with rheumatoid arthritis-multicenter analysis using FIT-RA registry-

Hiraku Motomura<sup>1</sup>, Isao Matsushita<sup>1</sup>, Kazunori Yamada<sup>2</sup>, Takashi Murayama<sup>3</sup>, Satoshi Nakazaki<sup>3</sup>, Shinichi Kato<sup>4</sup>, Hiroshi Fujinaga<sup>5</sup>, Haruki Takagi<sup>6</sup>, Tomoatsu Kimura<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Faculty of Medicine, University of Toyama, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Kanazawa University, <sup>3</sup>Rheumatology, Kanazawa Juhoku Hospital, <sup>4</sup>Rheumatology, Kamiaraya Clinic, <sup>5</sup>Department of Japanese Oriental Medicine and Rheumatology, Toyama Prefectural Central Hospital, <sup>6</sup>Department of Orthopaedic Surgery, Fukui Red Cross Hospital

Conflict of interest: None

[Objectives] To evaluate the retention rate at three year abatacept therapy for patients with rheumatoid arthritis (RA). [methods] We enrolled 148 patients with RA who were treated by abatacept and extracted from FIT (Fukui, Ishikawa, Toyama)-RA database of multi-center study group in Hokuriku area. Forty-nine patients did not received biologics (bio-naïve group) and 99 received other biologics previously (switching group). Seventy-eight patients (47.3%) received concomitant MTX. [Results] Fifty seven patients withdrew from abatacept treatment during three years. Thirty-one patients discontinued due to insufficient efficacy and 14 patients discontinued due to adverse events. The retention rate in bio-naïve and switching group were 66.4% and 41.0%, respectively. The retention rate of bio-naïve group was significantly higher than that in switching group. The retention rates of patients with or without concomitant MTX were 53.1% and 43.3% respectively. There was no significant difference between two groups. [Conclusion] Abatacept therapy for biologics naïve patients could be expected high retention rate. The combination of MTX might not significantly affect the retention rate of abatacept therapy.

### W36-4

#### The long term efficacy and safety of abatacept treatment in Bio-naïve and Bio-switch patients in the TBC registry: 3-year outcomes

Masahiro Hanabayashi<sup>1</sup>, Nobunori Takahashi<sup>2</sup>, Toshihisa Kojima<sup>3</sup>, Atsushi Kaneko<sup>3</sup>, Daihei Kida<sup>3</sup>, Hiroyuki Miyake<sup>1</sup>, Yutaka Yokota<sup>1</sup>, Yuji Hirano<sup>4</sup>, Shinya Hirabara<sup>4</sup>, Masatoshi Hayashi<sup>5</sup>, Yuichiro Yabe<sup>6</sup>, Takeshi Oguchi<sup>7</sup>, Fumiaki Sugiura<sup>7</sup>, Naoki Fukaya<sup>8</sup>, Yasuhide Kanayama<sup>9</sup>, Hideki Takagi<sup>11</sup>, Takayoshi Fujibayashi<sup>10</sup>, Naoki Ishiguro<sup>2</sup>

<sup>1</sup>Department of Orthopedic Surgery, Ichinomiya Municipal Hospital, Ichinomiya, Japan, <sup>2</sup>Department of Orthopedic Surgery and Rheumatology, Nagoya University Graduate School of Medicine, Nagoya, Japan, <sup>3</sup>Dept. of Orthop. Surg. and Rheumatology, Nagoya Medical Center, Nagoya, Japan, <sup>4</sup>Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan, <sup>5</sup>Department of Orthopedic Surgery, Nagano Red Cross Hospital, Nagano, Japan, <sup>6</sup>Department of Rheumatology, Tokyo Shinjuku Medical Center, Tokyo, Japan, <sup>7</sup>Department of Orthopedic Surgery and Rheumatology, Anjo Kosei Hospital, Anjo, Japan, <sup>8</sup>Department of Orthopedic Surgery, Kariya Toyota General Hospital, Kariya, Japan, <sup>9</sup>Department of Orthopedic Surgery, Toyota Kosei Hospital, Toyota, Japan, <sup>10</sup>Department of Orthopedic Surgery, Konan Kosei Hospital, <sup>11</sup>Department of Orthopedic Surgery, Nagoya Central Hospital, Nagoya, Japan

Conflict of interest: Yes

[Objectives] The aim of this study was to assess the 3-year outcomes of ABT therapy in biologic naïve patients (Naïve group) and patients failed to prior biologics (Switch group) in clinical routine practice. [Methods] 455 RA patients who underwent ABT treatment at Nagoya University Hospital and 20 other institutes (TBCR study group) were enrolled in this study. We compared disease activities using DAS28 CRP between Naïve group (n=262) and Switch group (n=193). Furthermore, discontinuation due to inadequate responses (IRs) and adverse events (AEs) were evaluated. [Results] Drug retention rate at 3-year was 78.2% in Naïve group and 59.1% in Switch group. Discontinuation rate due to IRs in Naïve group was lower than that in Switch group (8.0% vs. 22.8%), whereas discontinuation rate due to AEs were quite similar (4.6% vs. 7.3). In Switch group, we confirmed no differences in clinical responses and retention rate among the numbers of prior biologics. [Conclusion] This study demonstrated the long term efficacy and safety of

ABT in clinical routine practice. Our results suggest that ABT would be beneficial for biologic naïve patients and patients failed to prior biologics.

### W36-5

#### The study of trying to avoidance of secondary failure on the therapy of Biologics in rheumatoid arthritis

Motohiro Oribe

Oribe Clinic of Rheumatism and Medicine

Conflict of interest: None

[Objective] Approximately one-third of patients fail TNF- $\alpha$  antagonists or IL6 antagonist due to adverse effects or lack of efficacy, and there are limited treatment options available to these patients. Therefore the way of avoidance of Biologics secondary failure is meaningful. [Methods] 21 patients with 6 males and 15 females who initially responded anti TNF $\alpha$  or anti IL6 biologics at least 6 months or over were enrolled in this study. Average age and duration were 62 years and 13 years. Abatacept was started 0 week and 2 weeks later depending on the patients body weight 500mg or 750mg per 30 minutes after quit of biologics administered so far. Then same biologics were restarted 2 weeks later after last abatacept administered. Rheumatoid activity was assessed by DAS28CRP at 3 months and 6 months later. [Results] DAS28CRP was significantly improved at 3 months later to 3.17 from 4.14 (p<0.01) and at 6 months later to 2.62 (p<0.01). The effectiveness was not so difference with anti TNF $\alpha$  agents and anti IL6 agents although the effect was somewhat week in anti IL6 agents. [Conclusion] Abatacept can reset the effect of anti TNF $\alpha$  and anti IL6 biologics once fall into secondary failure by using long period.

### W36-6

#### Treatment of biological agents for the over 80 years old patients with rheumatoid arthritis

Wataru Shimada<sup>1</sup>, Hiraku Kikuchi<sup>1</sup>, Yasunori Itoh<sup>1</sup>, Harutoshi Tsujimoto<sup>2</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Sakai Hospital Kinki Faculty of Medicine, <sup>2</sup>Department of Rehabilitation, Sakai Hospital Kinki Faculty of Medicine

Conflict of interest: None

[Objectives] We evaluated the first clinical trial from patients with rheumatoid arthritis over 80 years old using Biologic agents. [Methods] 194 RA patients (M: 37, F: 157. 14-90 yo.) were treated with biological agents. We evaluated comparison under 79 yo. to over 80 yo. according to the kinds of biologics and others, clinical results, adverse effects and so on. [Results] Over 80 yo. group (M: 3, F: 21) used biologics (ETN: 54%, IFX: 4%, ADA: 4%, TCZ: 4%, ABT: 33%) and under 79 yo. group were (ETN: 35%, IFX: 17%, ADA: 8%, TCZ: 10%, ABT: 25%, GLM: 2%, CZP: 1%). Survival rate for biologics on 52 weeks, over 80 continued 73%, under 79 were 75% who received clinical remission. Rate of the biological mono-therapy were 25% in over 80, 18% in under 79. Rate of the full dose were 33% in over 80, 77% were in under 79. [Conclusion] Biological trials for over 80 yo. RA patients performed clinical results as same as under 79 yo.

### W37-1

#### Influence of biologic agents for bone mineral density in rheumatoid arthritis patients from Airtight study

Masahiro Tada<sup>1</sup>, Tatsuya Koike<sup>2,3</sup>, Kenji Mamoto<sup>1</sup>, Kentaro Inui<sup>1</sup>, Yuko Sugioka<sup>3</sup>, Tadashi Okano<sup>1</sup>, Hiroaki Nakamura<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Osaka City University Medical School, Osaka, Japan, <sup>2</sup>Search Institute for Bone and Arthritis Disease (SINBAD), Wakayama, Japan, <sup>3</sup>Center for Senile Degenerative Disorders (CSD), Osaka City University Medical School, Osaka, Japan

Conflict of interest: None

[Objectives] It was controversial that biologic agents increase the bone mineral density (BMD) for rheumatoid arthritis (RA) patients. We researched the influence for BMD according to the each biologics.

[Methods] We performed prospective study (Airtight study) to investigate the effects of Abatacept (ABT) for bone metabolism. Total 165 RA patients (pts) were divided into ABT group (50 pts) and Non-ABT group (115 pts). Non-ABT group contained INF (15 pts), ETN (22 pts), ADA (38 pts), TCZ (26 pts), and GLM (14 pts). We evaluated the percent change of BMD (% $\Delta$ BMD) of lumbar and femoral neck by using Dual-energy X-ray absorptiometry. [Results] In this study, 64% of ABT and 72% of Non-ABT completed biologics therapy for one year, with no significant difference ( $p=0.387$ ). There were no significant differences about BMD of lumbar and femoral neck in background. In % $\Delta$ BMD of lumbar, no significant difference was observed (ABT:  $-0.40\pm 4.31\%$ , Non-ABT:  $-1.67\pm 5.07\%$ ,  $p=0.524$ ). Whereas, the increase of femoral neck BMD was significantly higher in ABT ( $0.97\pm 8.63\%$ ) compared to Non-ABT ( $-2.19\pm 5.49\%$ ) ( $p=0.0471$ ). [Conclusion] It was revealed that the increase of femoral neck BMD in ABT group was significantly superior to that in Non-ABT group. ABT may have good efficacy for bone metabolism in RA patients.

### W37-2

#### The efficacy and adverse events of abatacept in patients with rheumatoid arthritis associated with autoimmune diseases

Yoshifumi Tada<sup>1</sup>, Rie Suematsu<sup>1</sup>, Satoko Tashiro<sup>1</sup>, Nobuyuki Ono<sup>1</sup>, Yuri Sadanaga<sup>1</sup>, Yukihide Ono<sup>1</sup>, Yukiko Tokuda<sup>1</sup>, Syuichi Koarada<sup>1</sup>, Akihide Ohta<sup>2</sup>

<sup>1</sup>Department of Rheumatology, Faculty of Medicine, Saga University, <sup>2</sup>Department of Nursing, Faculty of Medicine, Saga University

Conflict of interest: None

[Objectives] It has been shown that Abatacept (ABT) is effective in patients with RA associated with SLE. We investigated the characteristics and results of autoimmune disease-associated RA (AA-RA) patients treated with ABT. [Methods] Patients characteristics, efficacy, and adverse events were retrospectively investigated in patients with AA-RA and other RA (NAA-RA), who were treated with ABT. [Results] Eleven AA-RA patients (SLE 6, Sjogren's syndrome 3, dermatomyositis 1, myasthenia gravis 1) and 29 NAA-RA patients were studied. NAA-RA group were younger, more female dominant, shorter duration of arthritis, and less stage III/IV patients. Fewer patients in AA-RA had previous biological therapy, and the mean prednisolone dosage were higher in AA-RA. At 6 month, both groups showed similar continuation rates and DAS28CRP reduction. The rates of discontinuation due to adverse events, hospitalization, and hospitalization due to infection, were similar in two groups. AA-RA group showed more skin events (19/100 person-years vs 2.3/100 person-years), liver damage (25/100 person-years vs 6.8/100 person-years), and leucopenia (13/100 person-years vs 0/100 person-years). [Conclusion] AA-RA and NAA-RA showed similar efficacy and continuation rate, but AA-RA showed more adverse events.

### W37-3

#### Safety and drug retention rates of receptor agents and monoclonal antibody agents

Kenichiro Tokunaga<sup>1</sup>, Kazuki Yoshida<sup>2</sup>, Naoho Takizawa<sup>1</sup>, Masahiro Minoda<sup>1</sup>, Hideto Oshikawa<sup>1</sup>, Mitumasa Kishimoto<sup>3</sup>, Kazuo Matsui<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Kamada Medical Center, Kamogawa City, Chiba, Japan, <sup>2</sup>Department of Epidemiology Harvard School of Public Health, Boston, United States, <sup>3</sup>Immuno-Rheumatology Center, St. Luke's International Hospital, Tokyo, Japan

Conflict of interest: None

[Objectives] To clarify the potential differences in safety and drug retention of receptor-type biological disease-modifying antirheumatic drugs (bDMARDs) (CEPTs) and monoclonal antibody-type bDMARDs (MABs) in typical clinical practice. [Methods] The cohort (CABUKI) is a registry of all bDMARD users at the Department of Rheumatology, Kamada Medical Center 2003-2013. In this study, we compared the occurrence of serious adverse events (SAE) and drug retention rates between CEPTs (etanercept and abatacept) and MABs (adalimumab, certolizumab, infliximab, golimumab, and tocilizumab). [Results] There were 355 bDMARDs initiation episodes in the registry. We used 336 initiators with sufficient information. 211 were MABs whereas 125 were CEPTs. Sever-

al baseline characteristics were significantly different between groups: higher age, lower methotrexate dose, lower glomerular filtration rate, and more hypertension patients in CEPTs. Proportions free of SAE were 84.6% for MABs and 84.5% for CEPT. Drug retention rates at 1 year were 47.2% for MABs and 62.7% for CEPTs (hazard ratio of discontinuation 1.13 (95% confidence interval 0.87, 1.48) for MABs). [Conclusion] There was not statistically significant differences in safety between CEPTs and MABs. And drug retention rate of them were equivalent.

### W37-4

#### Relevance of expression of costimulatory molecules on peripheral helper T cells in pathogenesis of rheumatoid arthritis (RA)

Shunsuke Fukuyo, Shingo Nakayamada, Satoshi Kubo, Maiko Yoshikawa, Yusuke Miyazaki, Kazuhisa Nakano, Kazuyoshi Saito, Yoshiya Tanaka  
University of Occupational and Environmental Health, Japan

Conflict of interest: None

[Objectives] Costimulatory molecules such as CD28 and ICOS are essential for T cell activation. However, little is known its role in pathogenesis in RA. [Methods] We analyzed the T cell phenotype of CD4<sup>+</sup>CD28<sup>+</sup> or CD4<sup>+</sup>ICOS<sup>+</sup> cells and its pathological relevance in RA patients (n=48) before treatment and the change of proportion of them at 52 week after ABT (n=16) or TNF inhibitor (n=26) treatment. [Results] The proportion of Tfh and Th1 in CD4<sup>+</sup>CD28<sup>+</sup> cells were correlated with RF, ACPA and MMP-3 and that of Th17 in CD4<sup>+</sup>ICOS<sup>+</sup> cells correlated with ESR. The proportion of T17 and Tfh in CD4<sup>+</sup>CD28<sup>+</sup> cells decreased after ABT treatment, whereas Th17 increased after TNF inhibitor treatment. The proportion of T17 in CD4<sup>+</sup>ICOS<sup>+</sup> cells were decreased after ABT treatment, but not changed after TNF inhibitor treatment. The baseline proportion of Th1 was higher in patients who failed to achieve a remission at 52 week after treatment. The proportion of Th1 was not changed in both groups. [Conclusion] These results imply that CD4<sup>+</sup>CD28<sup>+</sup> Th1/Tfh and ICOS<sup>+</sup> Th17 associated with disease activity, which are the target of ABT treatment. Since CD4<sup>+</sup>CD28<sup>-</sup> or ICOS<sup>-</sup> Th1 did not affected by ABT, the presence of those subsets might be predictive of ABT treatment resistance.

### W37-5

#### Single-center observational study of rheumatoid arthritis (RA) with Tofacitinib in clinical practice

Atsushi Ihata<sup>1</sup>, Koji Kobayashi<sup>2</sup>, Atsumu Osada<sup>2</sup>, Shohei Nagaoka<sup>2</sup>

<sup>1</sup>Department of Rheumatology and Infectious Disease, Yokohama Minami Kyousai Hospital, Yokohama, Japan, <sup>2</sup>Department of Rheumatology, Yokohama Minami Kyousai Hospital, Yokohama, Japan

Conflict of interest: None

[Objectives] To examine the effect of tofacitinib, patient profile and adverse events in patients of RA with tofacitinib. [Methods] Retrospective observational study for 23 cases of RA treated with tofacitinib. [Results] The induction age was  $67.1\pm 2.9$  y.o. male was 26%. Disease duration was  $11.0\pm 2.2$  years. Steinblocker's staging was (4/7/6/6), and function class was (3/16/4/0) respectively. RF was  $207\pm 100$  and 2 cases were negative. ACPA positive rate was 66.7%. 83.6% were used with MTX and dose was  $11.8\pm 0.8$  mg weekly. The usage of corticosteroid was 34.8%. Other biologics were used before tofacitinib in 15 cases (9/4/2) and 8 cases were biologics naive. DAS28 (ESR) was  $5.1\pm 0.3$ , and SDAI was  $20.6\pm 2.5$ . 36 weeks later, DAS28 (ESR) was  $2.7\pm 0.2$  and SDAI was  $0.5\pm 0.1$ . Remission rate of SDAI was 23.5% at 4 week, 75% at 12 week and 100% at 20 week respectively. Dosage of corticosteroid was reduced by 37%. Adverse events were observed in 34.8% of patients. 3 cases were discontinued tofacitinib. An incident rate of HZV was 1/73.3 cases months. [Conclusion] Tofacitinib was effective for patients with high activity and resistant to other biologics. Tofacitinib rapidly achieve clinical remission as same as other biologics. However, serious adverse events to quit tofacitinib were observed.

### W37-6

#### Efficacy and safety of tofacitinib treatment in patients with rheumatoid arthritis

Naoki Iwamoto<sup>1</sup>, Sosuke Tsuji<sup>1</sup>, Shoichi Fukui<sup>1</sup>, Masataka Umeda<sup>1</sup>, Ayako Nishino<sup>1</sup>, Yoshikazu Nakashima<sup>1</sup>, Takahisa Suzuki<sup>1</sup>, Yoshiro Horai<sup>1</sup>, Tomohiro Koga<sup>1</sup>, Shin-ya Kawashiri<sup>1,2</sup>, Kunihiro Ichinose<sup>1</sup>, Yasuko Hirai<sup>1</sup>, Mami Tamai<sup>1</sup>, Hideki Nakamura<sup>1</sup>, Tomoki Origuchi<sup>3</sup>, Kiyoshi Migita<sup>4</sup>, Yukitaka Ueki<sup>2</sup>, Atsushi Kawakami<sup>1</sup>

<sup>1</sup>Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, <sup>2</sup>Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, <sup>3</sup>Nagasaki University School of Health science, Nagasaki University, Nagasaki, Japan, <sup>4</sup>National Hospital Nagasaki Medical Center, <sup>5</sup>Sasebo Chuo Hospital

Conflict of interest: None

[Objectives] To evaluate the efficacy and safety of tofacitinib (TOF) treatment in rheumatoid arthritis. [Methods] 17 patients with RA who were treated with TOF were enrolled. The patients continuing TOF treatment from clinical trial were not enrolled. Clinical disease activity as DAS 28-ESR, DAS28-CRP, SDAI and CDAI were assessed during of TOF treatment. [Results] All patients had been treated with biologics prior to TOF (mean 3 biologics). 8 patients (47.1%) received concomitant MTX with mean dose of 8.75mg/week. The mean DAS28-ESR score decreased from 5.32 to 4.17 at 12 weeks. In the concomitant MTX (+) and (-), DAS28-ESR score decreased from 5.86 to 4.23, and from 4.45 to 3.66, respectively. 3 patients discontinued TOF. All reason of discontinuation is lack of efficacy. [Conclusion] Even in the previous biologics treatment, without concomitant MTX, TOF treatment was effective in RA.

### W38-1

#### The effect of Abatacept on the progression of structural damage in patients with rheumatoid arthritis and poor prognostic factors

Yutaka Yokota<sup>1</sup>, Hiroyuki Miyake<sup>1</sup>, Masahiro Hanabayashi<sup>1</sup>, Daihei Kida<sup>2</sup>

<sup>1</sup>Ichinomiya Municipal Hospital, <sup>2</sup>Nagoya Medical Center

Conflict of interest: None

[Objectives] Assess the effects of Abatacept (ABT) on the progression of structural damage in 66 patients with rheumatoid arthritis who started treatment from October 2010 to May 2012 at two centers. Their joint damage score was assessed using the modified total Sharp score (mTSS) at baseline and after 48 weeks. [Methods] 50 patients were female. Mean age was 70.7 years. Biological agents naïve and switch were 46 patients and 18 patients, respectively. Changes of mTSS ( $\Delta$ mTSS) were compared between high and low scores groups at RF, anti cyclic citrullinated protein (anti CCP) and mHAQ. Furthermore, changes of mTSS were compared between moderate disease activity (MDA) and high disease activity (HDA) groups at DAS28-ESR. [Results] Mean DAS28-ESR at baseline was 5.25. Mean RF was 173.3IU/ml, Mean anti CCP was 333.2U/ml. Mean modified HAQ was 0.72. We could assess anti CCP in only 33 patients. Mean  $\Delta$ TSS was 0.47. Structural remission rate at week 48 was 69.6%. There was no significance about  $\Delta$ mTSS between low score group and high score group at RF and mHAQ. There was no significance about  $\Delta$ mTSS between MDA group and HDA group at DAS28-ESR. In anti CCP,  $\Delta$ mTSS of high score group was lower than that of low score group. [Conclusion] ABT therapy was effective for rheumatoid arthritis with poor prognostic factors.

### W38-2

#### Abatacept might be effective for the suppression of synovial inflammation and structural damage in the patients with rheumatoid arthritis

Kenji Mamoto<sup>1</sup>, Tatsuya Koike<sup>2,3</sup>, Tadashi Okano<sup>1</sup>, Yuko Sugioka<sup>2</sup>, Masahiro Tada<sup>1</sup>, Kentaro Inui<sup>4</sup>, Hiroaki Nakamura<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Osaka City University Medical School, Osaka, Japan, <sup>2</sup>Center for Senile Degenerative Disorders (CSDD), Osaka City University Medical School, Osaka, Japan, <sup>3</sup>Search Institute for Bone and Arthritis Disease (SINBAD), Wakayama, Japan, <sup>4</sup>Department of Rheumatology, Osaka City University Medical

School, Osaka, Japan

Conflict of interest: None

[Objectives] The aim of this study was to assess the effectiveness of abatacept (ABT) compared to tumor necrosis factor inhibitors (TNFi) for rheumatoid arthritis (RA) treatment. [Methods] This study included RA patients treated with ABT (n=38) or TNFi (n=72). They underwent clinical, laboratory, and ultrasonographic (US) assessment. The GS (Gray scale) and PD (Power Doppler) signals were scored in 26 synovial sites (22 joints). And radiographic damage was evaluated using van der Heijde modified total Sharp score (TSS). [Results] TNFi group showed significantly lower DAS score compared to baseline at 2 months. However, the improvement of DAS from baseline in ABT group was not significant at 2 months. Although there was no significant difference in DAS score at baseline between two groups, TNFi group showed lower DAS score than ABT group from 2 to 12 months. The sums of GSUS and PDUS scores at 6 and 12 months were lower than baseline in both groups, and showed no significant difference between two groups.  $\Delta$ TSS/year also showed no difference between two groups. [Conclusions] The clinical effect of ABT was inferior to TNFi. However, in the suppression of synovial inflammation and structural damage, the effect of ABT was not inferior to TNFi.

### W38-3

#### The effect of Abatacept for the bone resorption in patients with rheumatoid arthritis using the change of bone metabolic markers and modified total sharp scores

Motohiro Suzuki<sup>1</sup>, Yukihiko Matsuyama<sup>1</sup>, Noriyoshi Ogawa<sup>2</sup>, Daisuke Suzuki<sup>2</sup>, Hiroyuki Ohashi<sup>3</sup>, Seiji Tsuboi<sup>4</sup>, Taro Karahashi<sup>5</sup>, Toshiaki Miyamoto<sup>6</sup>, Yasuhiro Ohta<sup>7</sup>, Kaori Kobori<sup>8</sup>, Masakatsu Hayakawa<sup>9</sup>, Yoshinori Goto<sup>10</sup>

<sup>1</sup>Orthopaedics Surgery, Hamamatsu University School of Medicine, Shizuoka, Japan, <sup>2</sup>3rd Internal Medicine, Hamamatsu University School of Medicine, Shizuoka, Japan, <sup>3</sup>Internal Medicine, Omaezaki City Hospital, Shizuoka, Japan, <sup>4</sup>Rheumatology, Shizuoka Kosei Hospital, Shizuoka, Japan, <sup>5</sup>Rheumatology, Fujieda General Hospital, Shizuoka, Japan, <sup>6</sup>Rheumatology, Seirei Hamamatsu Hospital, Shizuoka, Japan, <sup>7</sup>Yasuhiro Clinic, <sup>8</sup>Kobori Orthopaedic Clinic, <sup>9</sup>Hayakawa Clinic, <sup>10</sup>Goto Internal Medicine Clinic

Conflict of interest: None

[Objectives] Recently, the possible role of Abatacept (ABT) on the regulation of osteoclast has been reported in RA. We studied the effect of ABT for the bone resorption in patients with RA by analyzing the changes in bone metabolic markers and radiograph. [Methods] Sixty three patients with RA (mean age: 62.0 y.o.) were studied. We measured CRP as the index of inflammation of RA, and pyridinoline (PYD) and deoxypyridinoline (DPD) as markers of bone resorption proper to treatment, 3, 6 and 12M after ABT therapy. We check the modified total Sharp Score (mTSS) at baseline and 12M. [Results] PYD and DPD reflected the mTSS of both baseline and 12M, but did not reflect the change of mTSS. The subgroup with decline of PYD and DPD at 3M (n=15) did not show the significant change in CRP. On the other hand, the subgroup with increased PYD and DPD at 3M (n=18) showed the significant improvement of CRP. Both subgroups showed significant improvement of CRP after 6M. [Conclusion] The change of PYD and DPD did not reflect the inflammation of RA at least at first 3M after ABT therapy suggests the possibility of the direct effect of ABT for the bone resorption in RA.

### W38-4

#### Abatacept can be used safely for RA patients with interstitial lung disease

Tamao Nakashita, Akira Jibatake, Kotaro Matsumoto, Akira Yoshida, Yuto Hamada, Shinji Motojima

Kameda Medical Center, Rheumatology and Allergy, Kamogawa, Japan

Conflict of interest: None

Interstitial lung disease (ILD) associated with RA is a big concern in planning the treatment and can be a cause of death. We have reported that when TNF-inhibitors were applied to RA patients with ILD, exacerbation

of ILD was noticed in 24 % (14/58). Here we analyzed the effects of abatacept (ABT) on RA associated with ILD. Subjects were 18 patients with RA with ILD who were administered with ABT for longer than 52 weeks and analysis was done for the changes between 0 to 52 weeks. Chest CT scan was done before and at 52 weeks. CXR was taken every 12 weeks, and additional CT and CXR were taken as needed basis. All the patients completed 52 weeks administration and no-one abandoned ABT due to the exacerbation of ILD. We further attempted to analyze more in detail the CT images according to the method by Kondoh et al. (Respirology 2013), and obtained what % of lung fields have findings of ILD. All the abnormalities suggestive of ILD before and at 52 weeks were 13.1 +/- 12.2 (mean +/- SD) and 12.5 +/- 13.4, respectively, and no differences were found. Mean DAS28-ESR and SDAI decreased significantly from 4.54 +/- 1.37 to 2.99 +/- 0.92, and from 17.8 +/- 11.3 to 8.7 +/- 4.3, respectively. In conclusions, ABT can be used safely for RA patients with ILD.

### W38-5

#### **The Safety and Treatment Efficacy of Abatacept in Rheumatoid Arthritis Patients with Pulmonary Complications: from the Tsurumi Biologics Communication Registry (TBCR) Multicenter Study**

Shinya Hirabara<sup>1</sup>, Toshihisa Kojima<sup>2</sup>, Nobunori Takahashi<sup>2</sup>, Yuji Hirano<sup>1</sup>, Yuichiro Yabe<sup>4</sup>, Atsushi Kaneko<sup>3</sup>, Daihei Kida<sup>3</sup>, Yasuhide Kanayama<sup>7</sup>, Naoki Fukaya<sup>10</sup>, Seiji Tsuboi<sup>9</sup>, Hiroyuki Miyake<sup>12</sup>, Hideki Takagi<sup>5</sup>, Takeshi Oguchi<sup>6</sup>, Takayoshi Fujibayashi<sup>8</sup>, Masatoshi Hayashi<sup>11</sup>, Masahiro Hanabayashi<sup>12</sup>, Shuji Asai<sup>2</sup>, Tomonori Kobayakawa<sup>2</sup>, Naoki Ishiguro<sup>2</sup>

<sup>1</sup>Department of Rheumatology, Toyohashi Municipal Hospital, Aichi, Japan, <sup>2</sup>Department of Orthopedic Surgery, Nagoya University School of Medicine, Nagoya, Japan, <sup>3</sup>Department of Orthopedic Surgery and Rheumatology, Nagoya Medical Center, Nagoya, Japan, <sup>4</sup>Department of Rheumatology, Tokyo Shinjuku Medical Center, Tokyo, Japan, <sup>5</sup>Department of Orthopedic Surgery, Nagoya Central Hospital, Nagoya, Japan, <sup>6</sup>Department of Orthopedic Surgery, Anjo Kosei Hospital, Aichi, Japan, <sup>7</sup>Department of Orthopedic Surgery, Toyota Kosei Hospital, Aichi, Japan, <sup>8</sup>Department of Orthopedic Surgery, Konan Kosei Hospital, Aichi, Japan, <sup>9</sup>Department of Orthopedic Surgery, Shizuoka Kosei Hospital, Shizuoka, Japan, <sup>10</sup>Department of Orthopedic Surgery, Kariya Toyota General Hospital, Aichi, Japan, <sup>11</sup>Department of Orthopedic Surgery, Nagano Red Cross Hospital, Nagano, Japan, <sup>12</sup>Department of Orthopedic Surgery, Ichinomiya Municipal Hospital, Aichi, Japan

Conflict of interest: None

[Objectives] Abatacept (ABT) is often used in patients with pulmonary complications. In the present study, we examined the persistence rates and treatment effects of ABT in patients with pulmonary complications. [Methods] We divided 250 RA patients registered in the TBCR who used ABT for  $\geq 52$  weeks according to whether they had pulmonary complications (L group: n=32) or not (N group: n=218). We then compared the persistence rates, incidence of adverse events, and disease activity between the two groups. [Results] The persistence rates for 52 weeks were 73.1% and 74.3% in the L and N groups, respectively. Adverse events occurred in 1 (3.13%) and 7 (3.83%) patients in the L and N groups, respectively. No pulmonary complications occurred after ABT administration in the L group, but 2 patients in the N group had interstitial pneumonia. Mean DAS28-CRP significantly improved in both groups from 4.7 at ABT initiation to 3.2 at 52 weeks in the L group, and from 4.4 to 3.1 in the N group. [Conclusion] The safety, treatment effects, and persistence rates of ABT were similar among RA patients with and without pulmonary complications. Use of ABT is beneficial even in patients with pulmonary complications, under close consideration of the risks involved.

### W38-6

#### **Dynamic regulation of T helper cell phenotype by targeting therapy in rheumatoid arthritis**

Shingo Nakayamada, Satoshi Kubo, Maiko Yoshikawa, Yusuke Miyazaki, Naoki Yunoue, Kazuhisa Nakano, Kazuyoshi Saito, Yoshiya Tanaka  
The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health

Conflict of interest: None

[Objectives] The pathogenesis of rheumatoid arthritis (RA) consists of an immune abnormality associated with T-B cell interaction and inflammation with active synovitis. We investigated association between lymphocyte subsets in a correlation with clinical findings and responsiveness to biologic DMARD therapy. [Methods] PBMC were obtained from 87 RA patients and 19 healthy donors (HD). Lymphocyte phenotype was defined by flow cytometric analysis. [Results] The proportion of effector memory T cells, Tfh cells and effector B cells were higher in RA compared with HD. The frequency of Tfh cells was correlated with DAS28 and RF titer and that of plasmablast was correlated with DAS28, ESR and MMP-3. The proportion of Tfh clustered with that of plasmablast. Abatacept decreased the proportions of effector memory T cells which consisted of Tfh, Th1 and Th17 cells. In contrast, TNF inhibitors increased effector T cells mainly Th17 cells. [Conclusion] These results imply that TNF blockade and CD28 co-stimulation blockade may alter contradictory changes of lymphocyte phenotype, even though both treatments improve disease activity. Thus, abnormal regulation of lymphocyte differentiation independent of inflammation may underlie in the pathogenesis of RA.

### W39-1

#### **Comparison of the image of ultrasonography and synovium pathology of the joints in the patients with rheumatoid arthritis treated by biological agent**

Asami Abe, Hajime Ishikawa, Kiyoshi Nakazono, Akira Murasawa, Daisuke Kobayashi, Satoshi Ito  
Dept. of Rheumatology, Niigata Rheumatic Center

Conflict of interest: None

Objectives: The objectives of this study were to investigate whether the image of ultrasonography (US) at the operated joint reflect synovium pathology or clinical indicators, and to compare the results in the patient treated by non-biological agent (NonBio) and biological agent (Bio). Materials and methods: RA related orthopaedic surgery was performed at 493 joints including 5 shoulders, 43 knees, 36 elbows, 90 wrists, 75 fingers, 9 ankles and 43 toes. Preoperatively, US was performed and grade of Power Doppler (PD) signal was weighed. Rooney score, DAS28-ESR (4), MMP-3, CRP were investigated. Patients treated by Bio were IFX13, ETN22, TCZ18, ADA7, ABT1, GLM4, CZP3. Results: PDS, DAS28, MMP-3 and Rooney score in the patients treated by Bio were significantly lower than those in the patients treated by NonBio. Rooney score fibrosis in patients using IFX and TCZ were significantly higher than those in patients treated by NonBio. Synovocyte hyperplasia, three items of lymphocytes in patients treated IFX and TCZ were lower than those in patients treated by NonBio. Conclusion: The activity of RA synovitis at operated site was suppressed in patients treated by Bio. There were some differences in clinical data, pathological score, PDS and DAS among Bio.

### W39-2

#### **Impacts of Artificial Total Elbow Arthroplasty on Disease Activity and HAQ in Rheumatoid Arthritis associated with Biologics**

Ayako Kubota<sup>1</sup>, Masayuki Sekiguchi<sup>1</sup>, Takashi Nakamura<sup>1</sup>, Yoshiyasu Miyazaki<sup>1</sup>, Ryo Takamatssu<sup>1</sup>, Toyomitsu Tsuchida<sup>2</sup>, Toru Suguro<sup>3</sup>  
<sup>1</sup>Department of Orthopaedic Surgery, Toho University School of Medicine, Tokyo, Japan, <sup>2</sup>Tsuchida Clinic, <sup>3</sup>Japan Research Institute of Artificial Joint

Conflict of interest: None

[Objectives] We examine impacts of TEA on postoperative disease activity, range of motion, HAQ and Mayo Elbow Performance Score (MEPS) in RA patients using biologics. [Methods] In RA patients using biologics, 21 joints including 12 ETN, 5 TCZ, 2 ADA and 2 IFX for which TEA was performed from 2006 to 2014 were included. FINE Total elbow system was used for all cases. Disease activity was assessed by DAS 28-ESR and CDAI and functional disorder by HAQ and MEPS before and after surgery. [Results] Mean age and disease duration was 62.9 years old and 24.8 years. Disease activity significantly improved from 4.2 to 3.2 in DAS 28-ESR and 13.1 to 6.5 in CDAI respectively. Range of motion before and after surgery significantly improved from -35.2° to



-20° in extension, 116.0° to 134.3° in flexion, 52.4° to 68.1° in pronation and 69.4° to 78.3° in supination respectively. Improvement in HAQ was achieved in function items not only for upper limb but also lower limb. MEPS also significantly improved from 45.3 to 97.1. [Conclusion] With its availability to achieve better supportive property and range of motion of elbow joint, TEA achieved improvement in upper limb function. Further, TEA was useful for achieving lower limb function since elbow joint is a weight bearing joint in RA patients.

### W39-3

#### Biological agents do not increase perioperative complication of RA spine surgery

Kensuke Koyama, Hirota Haro

Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Yamanashi, Japan

Conflict of interest: None

[Objectives] To evaluate the risk of surgical site infection (SSI) in rheumatoid arthritis (RA) patients treated with biological agents (BIO) undergoing spine surgery. [Methods] This study included 39 RA patients who underwent spine surgery. Eight patients were treated with BIO [infliximab (3), adalimumab (1), tocilizumab (3), golimumab (1)], and 31 patients were treated with conventional disease-modifying antirheumatic drugs (DMARDs). The characteristics of the patients were mean age of 69.1 years, mean duration of illness was 14.3. 20 cases were used methotrexate, the mean dose of 5.8mg/week. We examined the incidence of perioperative adverse event (surgical site infection: SSI, delay wound healing) in BIO group and Non-BIO group. The statistical differences between each group were examined using Fisher's exact test. [Results] One case of SSI was observed in BIO group and 5 cases in Non-BIO group, but there was no statistically significant difference [P=1.000, OR: 0.743 (0.07-7.44)]. None case of delay wound healing was observed in BIO group and 2 cases in Non-BIO group [P=1.00, OR: 1.56 (0.03-15.9)]. [Conclusion] The risk of perioperative SSI in RA patients treated with biological agents undergoing spine surgery was not increased.

### W39-4

#### Deep infection following prosthetic surgery in patients with rheumatoid arthritis

Masayuki Azukizawa<sup>1</sup>, Hiromu Ito<sup>1</sup>, Moritoshi Furu<sup>1,2</sup>, Masahiro Ishikawa<sup>1,2</sup>, Hiroko Ogino<sup>1</sup>, Takahiro Iwata<sup>1</sup>, Yosuke Hamamoto<sup>1</sup>, Motomu Hashimoto<sup>2</sup>, Takao Fujii<sup>2,3</sup>, Noriyuki Yamakawa<sup>3</sup>, Chikashi Terao<sup>4</sup>, Wataru Yamamoto<sup>5</sup>, Tsuneyo Mimori<sup>2,3</sup>, Shuichi Matsuda<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Graduate School of Medicine, Kyoto University, <sup>2</sup>Department of the Control for Rheumatic Diseases, Graduate School of Medicine, Kyoto University, <sup>3</sup>Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, <sup>4</sup>Center for Genomic Medicine, Graduate School of Medicine, Kyoto University, <sup>5</sup>Medical Information Management Center, Kurashiki Sweet Hospital

Conflict of interest: None

[Objectives] The aims of the study were to investigate the postoperative deep prosthetic infection in RA patients treated in our institution and to clarify the risk factor of the deep infection after replacement surgery. [Methods] Data of all prosthetic replacement performed at our institution between January 2004 and October 2013 were collected postoperatively at more than six months. We examined whether they had suffered from prosthetic infection after surgery, and whether they had ever administered biological DMARD. We researched the postoperative prosthetic infection free rate. [Results] The mean follow-up period was 4.8 years. According to the Kaplan-Meier survival analysis, the cumulative prosthetic infection free rate in 3 months, in 1 year and in 3 years was 97.9%, 97.3%, and 96.2%, respectively. We analyzed a multivariate logistic regression analysis, diabetes mellitus (p = 0.031) and biological DMARD administration (p = 0.011) were significant independent factor for postoperative prosthetic joint infections. [Conclusion] These results suggest that administration of biological DMARD or diabetes mellitus is an independent risk factor of the postoperative prosthetic infections.

### W39-5

#### Clinical outcomes of arthroscopic synovectomy in rheumatoid arthritis with the biologic therapy

Ryozo Harada<sup>1</sup>, Keiichiro Nishida<sup>1,2</sup>, Kenzo Hashizume<sup>1</sup>, Yoshihisa Nasu<sup>3</sup>, Ryuichi Nakahara<sup>1</sup>, Takahiro Machida<sup>1</sup>, Masahiro Horita<sup>1</sup>, Toshifumi Ozaki<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, <sup>2</sup>Department of Human Morphology Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, <sup>3</sup>Kurashiki Sweet Hospital

Conflict of interest: None

[Objectives] We reviewed the results of arthroscopic synovectomy in patients with rheumatoid arthritis under the biologic therapy. [Methods] 12 joints underwent arthroscopic synovectomy (9 knees, 3 elbows) in 11 patients were included. The mean age of patients at the surgery was 52 years, the average disease duration was 7 years and the average follow-up period was 54 months. According to the Larsen grade, there were 5 cases in grade ~II, 7 in grade III~. The clinical evaluations included the levels of CRP, serum MMP-3, DAS28-CRP, HAQ, survival rate with the joint replacement surgery as the endpoint. Statistical analysis was performed using Wilcoxon signed-rank sum test and Kaplan-Meier method. [Results] The mean pre- and post-operative CRP was 1.6, 0.3 mg/dl (p=0.01), MMP-3 was 216, 137 ng/ml (p=0.20), DAS28-CRP was 3.69, 2.84 (p=0.08), HAQ was 0.61, 0.72 (p=0.28), respectively. 5 joint replacements (4 knees, 1 elbow) were done before the final follow-up. The 5-years survival rate was 52.4% in total, 100% in the Larsen grade ~II, and 28.6% in grade III~. [Conclusions] The arthroscopic synovectomy resulted in the poor clinical outcome with lower survival rate when indicated to the joint with Larsen grade III and IV, even in the patients with lower disease activity controlled by biologic agents.

### W39-6

#### Concomitant methotrexate as an independent predictor of total knee arthroplasty in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors

Shuji Asai, Toshihisa Kojima, Nobunori Takahashi, Koji Funahashi, Yutaka Yoshioka, Toki Takemoto, Kenya Terabe, Nobuyuki Asai, Naoki Ishiguro

Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

Conflict of interest: Yes

[Objectives] This study aimed to identify predictors of total knee arthroplasty (TKA) in patients with rheumatoid arthritis (RA) treated with tumor necrosis factor inhibitors (TNFi). [Methods] A total of 155 patients with RA received TNFi between May, 2005 and May, 2008 at our institute. 68 patients (111 knees) who had symptomatic (tender and/or swollen) knee at the initiation of TNFi (baseline) were included in this study. The impact of variables at baseline on the incidence of TKA was assessed with Cox proportional hazards models. [Results] Patients were predominantly female (86.8%), and had a median age of 55 years, disease duration of 8 years and DAS28-CRP of 5.5. 50 (73.5%) patients received concomitant methotrexate (MTX). Pre-existing joint damages were evaluated using Larsen grade: grade 0, 5 knees; grade 1, 24 knees; grade 2, 27 knees; grade 3, 31 knees; grade 4, 24 knees. Multivariate analysis revealed that older age (hazard ratio [HR]: 1.04 per 1 year, 95% confidence interval [CI]: 1.01 to 1.08), Larsen grade (HR: 2.70 per 1 grade, 95% CI: 1.82 to 4.00) and concomitant MTX (HR: 0.45, 95% CI: 0.22 to 0.89) independently predicted TKA. [Conclusion] Older age, Larsen grade and concomitant MTX at baseline are independent predictors of TKA in patients with RA treated with TNFi.

### W40-1

#### Role of sphingosine-1-phosphate-3 (S1P3) receptor signalling in murine collagen-induced arthritis model

Hidetake Nagahara<sup>1</sup>, Masataka Kohno<sup>1</sup>, Ken Murakami<sup>1</sup>, Amame Nakabayashi<sup>1</sup>, Yuji Kukida<sup>1</sup>, Kazuki Fujioka<sup>1</sup>, Wataru Fujii<sup>1</sup>, Takahiro Seno<sup>1,2</sup>, Aihiro Yamamoto<sup>1</sup>, Ryo Oda<sup>3</sup>, Daisaku Tokunaga<sup>3</sup>, Toshikazu

Kubo<sup>2</sup>, Yutaka Kawahito<sup>1</sup>

<sup>1</sup>Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>2</sup>Department of Rheumatic Diseases and Joint Function, Kyoto Prefectural University of Medicine, <sup>3</sup>Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine

Conflict of interest: None

[Objectives] To examine the role of S1P3 receptor signaling in the development of collagen-induced arthritis (CIA) in murine. [Methods] Wild-type (WT) and S1P3-deficient (KO) mice were immunized with bovine type II collagen, and disease severity were scored assessed by arthritis scoring system of 0–4. Their paws were stained with H&E. Histopathological changes were scored based on synovial inflammation, cartilage destruction and bone erosion parameters of 0–3. Blood was collected and the levels of anti-type II collagen antibodies were measured. Total RNA was obtained from synoviocytes which were stimulated with TNF $\alpha$  for 2hrs, and we evaluated the expression of S1P3 receptor with real-time PCR. [Results] S1P3 KO mice showed significantly lower arthritis severity score compared with WT mice ( $P < 0.05$ ). Histopathological evaluation of paws showed marked reductions in synovial inflammation and bone erosion parameters in S1P3 KO mice compared with WT mice ( $P < 0.05$ ). The level of anti-type II collagen antibodies were not different between two groups. The expression of S1P3 mRNA level in mice synoviocytes treated with TNF $\alpha$  was significantly upregulated. [Conclusion] These results indicate that S1P3 receptor signaling plays an important role in the development of murine CIA model.

#### W40-2

##### The analysis of autoimmune-like phenotypes in Allergy inhibitory receptor-1 deficient mice

Akira Iizuka<sup>1</sup>, Seiji Segawa<sup>1</sup>, Masahiro Tahara<sup>1</sup>, Shunta Kaneko<sup>1</sup>, Masahiro Yokosawa<sup>1</sup>, Yuya Kondo<sup>1</sup>, Shiro Shibayama<sup>2</sup>, Isao Matsumoto<sup>1</sup>, Takayuki Sumida<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Japan, <sup>2</sup>Department of Immunobiology, Faculty of Medicine, University of Tsukuba, Japan, <sup>3</sup>Tsukuba Institute ONO Pharmaceutical Co. LTD, Japan

Conflict of interest: Yes

[Objectives] Allergy inhibitory receptor-1 (Allergin-1) is known as an immune suppressive molecule. The purpose of this study is to clarify the role of Allergin-1 in autoantibody production. [Methods] 1) The expression of Allergin-1 in splenocytes from wild type (WT) mice was analyzed by flowcytometry. 2) WT and Allergin-1 deficient (Allergin-1<sup>-/-</sup>) mice were treated with dead cells derived from thymocytes. At 2, 4, 6, 8, 10 and 12 weeks after dead cells injection, the titer of anti-dsDNA and anti-Histone antibodies in serum was measured by ELISA. 3) At 12 weeks after dead cells injection, IgG and C3 deposition on glomerulus were analyzed by immunofluorescent staining. [Results] 1) Macrophages, neutrophils and dendritic cells expressed Allergin-1. 2) The titer of Anti-dsDNA and anti-Histone antibodies were significantly higher in Allergin-1<sup>-/-</sup> mice compared with WT mice 8 and 12 weeks. 3) In Allergin-1<sup>-/-</sup> mice, IgG deposition tended to be increased compared with WT mice. However, C3 deposition was not significantly different between WT and Allergin-1<sup>-/-</sup> mice. [Conclusion] Allergin-1 might play a crucial role in autoantibody production through macrophages, neutrophils and dendritic cells.

#### W40-3

##### MicroRNA-124 Inhibits the Progression of Adjuvant-induced Arthritis in Rats

Yuji Nakamachi<sup>1</sup>, Kenichiro Ohnuma<sup>1,2</sup>, Kenichi Uto<sup>1,2</sup>, Yoriko Noguchi<sup>1,2</sup>, Jun Saegusa<sup>1,2</sup>, Seiji Kawano<sup>2</sup>

<sup>1</sup>Department of Clinical Laboratory, Kobe University Hospital, Kobe, Japan, <sup>2</sup>Division of Laboratory Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

Conflict of interest: None

**Objective.** MicroRNAs are small endogenous, noncoding RNAs that act as post-transcriptional regulators. We analyzed the *in vivo* effect of miRNA-124 on adjuvant-induced arthritis (AIA) in rats. **Methods.** AIA was induced in Lewis rats by injecting incomplete Freund's adjuvant with heat-killed Mycobacterium tuberculosis. Precursor (pre)-miR-124 was injected into the right hind ankle on day 9. Morphological changes in the ankle joint were assessed by microCT and histopathology. Cytokine expression was examined by Western blotting and real-time RT-PCR. The effect of miR-124 on predicted target mRNAs was examined by luciferase reporter assays. The effect of pre-miR-124 on the differentiation of human osteoclasts was examined by TRAP staining. **Results.** We found that miR-124 suppressed AIA in rats, as demonstrated by decreased synoviocyte proliferation and bone destruction. Osteoclast counts and expression level of RANKL, ITGB1 and NFATc1 were reduced in AIA rats treated with pre-miR-124. Luciferase analysis showed that miR-124 directly targeted the 3'-UTR of the rat NFATc1, ITGB1, SP1, and CEBPA mRNAs. Pre-miR-124 suppressed the differentiation of human osteoclasts. **Conclusion.** miR-124a is a candidate for therapeutic use for human rheumatoid arthritis.

#### W40-4

##### CD4<sup>+</sup> T cells regulate the development of collagen induced arthritis in ROR $\gamma$ t Tg mice

Yuya Kondo<sup>1</sup>, Masahiro Tahara<sup>1</sup>, Mana Iizuka<sup>1</sup>, Masahiro Yokosawa<sup>1</sup>, Shunta Kaneko<sup>1</sup>, Seiji Segawa<sup>1</sup>, Hiroto Tsuboi<sup>1</sup>, Satoru Takahashi<sup>2,3</sup>, Isao Matsumoto<sup>1</sup>, Takayuki Sumida<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, <sup>2</sup>Department of Anatomy and Embryology, Faculty of Medicine, University of Tsukuba, <sup>3</sup>Laboratory Animal Resource Center, University of Tsukuba

Conflict of interest: None

[Objectives] To clarify the effect of ROR $\gamma$ t expression on T cells in the development of autoimmune arthritis. [Methods] 1) Incidence and severity of collagen induced arthritis (CIA) were assessed in C57BL/6 (B6) and ROR $\gamma$ t transgenic (ROR $\gamma$ t Tg) mice. 2) Transcription factors and chemokine receptor expression on collagen type II (CII) reactive CD4<sup>+</sup> T cells were analyzed by FACS. 3) Lymphocytes in foot joints were harvested after the induction of CIA, and examined by FACS. 4) Draining lymph node cells or CD4<sup>+</sup> cells isolated from B6 or ROR $\gamma$ t Tg mice were transferred into immunized B6 mice, and then clinical course of arthritis was assessed. [Results] 1) CIA was significantly suppressed in Tg mice. 2) Foxp3 expressing regulatory T cells (Treg) expressed ROR $\gamma$ t, and higher expression of CC chemokine receptor 6 (CCR6) was observed in Foxp3<sup>+</sup> Treg cells in ROR $\gamma$ t Tg mice. 3) CCR6<sup>+</sup>Foxp3<sup>+</sup> Treg cells tended to be increased in foot joints in ROR $\gamma$ t Tg mice. 4) Transfer of lymph node cells or CD4<sup>+</sup> cells harvested from ROR $\gamma$ t Tg mice significantly suppressed CIA in B6 mice. [Conclusion] Suppression of the development of CIA in ROR $\gamma$ t Tg mice might be related with the local inhibition by CCR6<sup>+</sup>ROR $\gamma$ t<sup>+</sup>Foxp3<sup>+</sup>Treg cells.

#### W40-5

##### Role of intestinal microbiota in the pathogenesis of organ-specific autoimmunity in lymphopenia-induced autoimmunity mouse model

Toshiki Eri<sup>1</sup>, Kimito Kawahata<sup>2</sup>, Ei Bannai<sup>1</sup>, Takehito Kanzaki<sup>3</sup>, Lisa Akahira<sup>1</sup>, Kazuya Michishita<sup>1</sup>, Kazuhiko Yamamoto<sup>1</sup>

<sup>1</sup>Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, <sup>2</sup>Department of Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, <sup>3</sup>Department of Internal Medicine, Yamanashi Prefectural Central Hospital, Yamanashi, Japan

Conflict of interest: None

[Objectives] Previously, we reported the role of intestinal microbiota in the proliferation of T<sub>H</sub> cells to promote antinuclear antibodies production in lymphopenia-induced autoimmunity. We would like to investigate the role of intestinal microbiota in the pathogenesis of long-term organ-specific autoimmunity in this mouse model to pave the way to the novel microbiological therapeutic approach to autoimmune diseases. [Methods] CD4<sup>+</sup>CD25<sup>-</sup> cells from wild-type BALB/c mouse are transferred into

athymic nude BALB/c mouse. Inflammation of organs and autoantibodies are observed during 5 months after transfer. Some nude mice are orally administrated broad-spectrum antibiotics including ciprofloxacin (C), imipenem (I), metronidazole (M) and vancomycin (V). [Results] Transferred nude mice developed gastritis, colitis, sialoadenitis and oophoritis at high rates. Combination of CIMV decreased the incidence of gastritis, colitis and oophoritis, but it exacerbated sialoadenitis. Single V inhibited the incidence of colitis and exacerbated the others. [Conclusion] Organ-specific autoimmunity in the lymphopenia-induced autoimmunity mouse model can be ameliorated or exacerbated by antibiotics. Further investigation is needed to detect specific microorganisms involved in the inflammation of each organ.

#### W40-6

##### IL-21 signaling for B cells plays critical roles in the development of collagen-induced arthritis

Koji Sakuraba<sup>1</sup>, Yukio Esaki<sup>1</sup>, Goh Hirata<sup>1</sup>, Satoshi Kamura<sup>1</sup>, Hiroataka Iura<sup>1</sup>, Masanari Ota<sup>1</sup>, Hisaaki Miyahara<sup>1</sup>, Hisakata Yamada<sup>2</sup>

<sup>1</sup>Orthopaedics Surgery and Rheumatology, Clinical Reserch Center, Kyushu Medical Center, National Hospital Organization, Fukuoka, Japan, <sup>2</sup>Division of Host Defense, Medical Institute of Bioregulation, Kyushu University

Conflict of interest: None

IL-21 is a T cell-derived cytokine whose receptor is expressed on variety of cells in immune system. IL-21 was reported to be involved in the development of Th17 cells and follicular helper T cells, as well as in antibody production of B cells, all of which could be involved in the development of autoimmune diseases. In order to clarify the roles of IL-21 signaling in the pathogenesis of autoimmune arthritis, we investigated the development of collagen-induced arthritis (CIA) in IL-21 receptor (IL-21R)-deficient mice. IL-21R-deficient or wild type (WT) C57BL/6 mice were immunized with chicken type II collagen (CII) emulsified in CFA on day 0 and were given boost injection with CII on day 21. We found that IL-21R-deficient mice were resistant to the development of CIA. CII-specific antibody production was severely impaired in IL-21R-deficient mice, which is consistent with the reduction of germinal center B cells. On the other hand, development of Th17 and Tfh cells was largely unaffected by the absence of IL-21 signaling. Thus, IL-21 signaling is critically involved in the development of CIA mainly by inducing pathogenic autoantibody production of B cells.

#### W41-1

##### The utility of estimated glomerular filtration rate calculated by serum cystatine C in patients with rheumatoid arthritis

Yukiko Nozawa<sup>1</sup>, Hiroe Sato<sup>1</sup>, Ayako Wakamatsu<sup>1</sup>, Chinatsu Takai<sup>1</sup>, Takeshi Nakatsue<sup>1</sup>, Naoki Kondo<sup>2</sup>, Yoko Wada<sup>1</sup>, Takeshi Kuroda<sup>3</sup>, Masaaki Nakano<sup>4</sup>, Ichiei Narita<sup>1</sup>

<sup>1</sup>Division of Clinical Nephrology and Rheumatology, Graduate School of Medical and Dental Sciences, Niigata University, <sup>2</sup>Division of Orthopedic Surgery Department of Regenerative and Transplant Medicine, Graduate School of Medical and Dental Sciences, Niigata University, <sup>3</sup>Health Administration Center, Niigata University, <sup>4</sup>School of Health Sciences, Faculty of Medicine, Niigata University

Conflict of interest: None

[Objectives] To evaluate the accuracy of estimated glomerular filtration rate (eGFR) calculated by serum creatinine (Cr) and cystatin C (cysC) in patients with rheumatoid arthritis (RA), accompanied by lower muscle mass and physical dysfunction. [Methods] Fourteen patients with RA who had been admitted to Niigata University Hospital were included in this study (3 males and 11 females, mean value of CK 40.4±29.9 IU/L, Steinbrocker functional class were 3 in all patients). Renal inulin clearance (Cin) was measured in each subject, and compared to estimated GFR using Cr (eGFR<sub>creat</sub>) or cysC (eGFR<sub>cys</sub>), and creatinine clearance×0.715 (Ccr). [Results] Mean eGFR<sub>creat</sub> was significantly higher than Cin ( $p=0.005$ ) (Cin, 58.3±26.9 ml/min/1.73m<sup>2</sup>; eGFR<sub>creat</sub>, 75.5±34.2 ml/min/1.73m<sup>2</sup>). The correlation coefficient of Cin and eGFR<sub>cys</sub> was higher than that of Cin and eGFR<sub>creat</sub> ( $r=0.933$ ,  $p<0.001$  vs.  $r=0.833$ ,  $p<0.001$ ). The ratio of eGFR<sub>creat</sub> to Cin was 1.32±0.31 (minimum

1.00-maximum 1.98), while that of eGFR<sub>cys</sub> to Cin was 0.98±0.24 (0.60-1.40). Patients with lower serum CK levels had a tendency to have higher ratio of eGFR<sub>creat</sub> to Cin ( $r=-0.524$ ,  $p=0.054$ ). [Conclusion] eGFR<sub>cys</sub> is useful for estimating accurate kidney function in RA patients, especially with low serum CK levels.

#### W41-2

##### Serum 14-3-3 $\eta$ reflect disease activity and therapeutic response in patients with rheumatoid arthritis

Kentaro Hanami<sup>1</sup>, Shintaro Hirata<sup>1</sup>, Anthony Marrotta<sup>2</sup>, Kaoru Yamagata<sup>1</sup>, Ippei Miyagawa<sup>1</sup>, Satoshi Kubo<sup>1</sup>, Shunsuke Fukuyo<sup>1</sup>, Norifumi Sawamukai<sup>1</sup>, Kazuhisa Nakano<sup>1</sup>, Shingo Nakayamada<sup>1</sup>, Kazuyoshi Saito<sup>1</sup>, Yoshiya Tanaka<sup>1</sup>

<sup>1</sup>The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, <sup>2</sup>Augurex Life Sciences Corp., North Vancouver, Canada

Conflict of interest: None

[Objectives] Novel biomarker is essential for better understanding of rheumatoid arthritis (RA). 14-3-3 $\eta$  is an intracellular chaperone protein, presenting in synovial fluid at high concentration in RA, suggesting relevance for pathogenesis. We assessed relationship between serum 14-3-3 $\eta$  and disease activity as well as therapeutic response in RA. [Methods] Serum 14-3-3 $\eta$  was measured with ELISA at initiation and after 1 year of treatment in 149 RA patients (adalimumab 49, MTX 23, tocilizumab 50, tofacitinib 27). Relationship between 14-3-3 $\eta$  and disease activity with several markers were assessed. [Results] Baseline characteristics (median) were: age 60.0 year, disease duration 51 months, DAS28-ESR 5.35, CDAI 22, SDAI 24.3, RF 60.4U/ml, ACPA 100U/ml, ESR 44mm/h. At baseline, 110 patients (74%) with 14-3-3 $\eta$  positive ( $\geq 0.19$ ) had higher disease activity than those with 14-3-3 $\eta$  negative; DAS28-ESR 5.6 vs. 4.8,  $p=0.01$ , CDAI 24.7 vs. 16.0,  $p=0.02$ , SDAI 26.8 vs. 18.8,  $p=0.02$ , RF 85 vs. 16,  $p<0.0001$ , ACPA 100 vs. 17,  $p=0.0002$ , ESR 48 vs. 35,  $p=0.05$ . At year-1, median 14-3-3 $\eta$  decreased from 0.7 to 0.37 ng/ml ( $p<0.0001$ ), with higher DAS28-ESR remission rate ( $p=0.0018$ ). [Conclusion] Serum 14-3-3 $\eta$  reflect disease activity and therapeutic response in RA.

#### W41-3

##### Relationship between rheumatoid factor and outcome measures of disease activity, functional disability, and affected joints in patients with rheumatoid arthritis: A nationwide multicenter observational cohort study based on the *NinJa* (National database of rheumatic diseases by IR-Net in JAPAN) 2013

Susumu Nishiyama<sup>1</sup>, Tetsushi Aita<sup>1</sup>, Yasuhiko Yoshinaga<sup>1</sup>, Shigeto Tohma<sup>2</sup>

<sup>1</sup>Rheumatic Disease Center, Kurashiki Medical Center, <sup>2</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami-hara National Hospital, National Hospital Organization, Sagami-hara

Conflict of interest: None

**Objective:** To study the relationship between RF and outcome measures. **Methods:** Total joint indices were calculated as described previously. <sup>1</sup> Patients with RA who had been registered and checked RF levels both in 2012 and 2013 were selected from *NinJa* database and data of 5902 patients were extracted. Patients were classified into three groups according to RF levels measured in 2012. **Results:** Both in 2012 and in 2013, levels of SDAI and HAQ had an upward trend and boolean remission rate had a downward trend as RF levels increased. There was statistical significance of outcome measures between any two groups of RF negative, low-positive, and high-positive.  $\Delta$ RF significantly correlated with  $\Delta$ SDAI and  $\Delta$ HAQ in RF positive patients. In multivariate analysis, only upper/small joint index among four joint regions significantly correlated with RF levels and change in upper/large joint index correlated with  $\Delta$ RF. **Conclusions:** Disease activity and physical function went worse as RF levels elevated. There was a significant correlation between change in RF and change in these outcome measures. RF levels correlated with upper/small joint involvement and change in RF correlated with change in affected joints in upper/large region. **Reference:** 1. Rheumatol Int. 2012; 32:2569-71

#### W41-4

##### MMP-3 as a biomarker of disease activity of rheumatoid arthritis

Yuko Uemura<sup>1</sup>, Goh Tsuji<sup>2</sup>, Yoshihide Ichise<sup>2</sup>, Ryosuke Umeda<sup>2</sup>, Sho Sendo<sup>2,3</sup>, Shunichi Kumagai<sup>1,2</sup>

<sup>1</sup>Institute for Medicine Research, Shinko Hospital, Kobe, Japan, <sup>2</sup>Department of Rheumatic Diseases, Shinko Hospital, Hyogo, Japan, <sup>3</sup>Department of Rheumatology and Clinical Immunology Hyogo, Japan

Conflict of interest: None

[Objects] To confirm the clinical significance of serum MMP-3 detection in evaluation of the disease activity of RA and effectiveness of the treatment. [Methods] MMP-3 was measured for 206 outpatients with RA during a period of 3 months, and also serially measured in RA patients treated with MTX and infliximab (IFX). [Results] Serum MMP-3 was significantly correlated with CRP, SAA, and ESR. MMP-3 was significantly correlated with DAS28 (CRP) (in female patients,  $p < 0.001$ ) and also with the EULAR criteria. The strongest association with MMP-3 was found to swollen joint count among the items of DAS28. Furthermore, MMP-3 levels increased with advances of Stage and Class of RA. 12 and 24 weeks after treatment with MTX, MMP-3 levels were gradually decreased ( $p = 0.0188$  and  $p = 0.0179$ ). The extent of the decrease was more prominent in patients with better response than those with poor response. MMP-3 levels significantly decreased 4, 12, 24, and 48 weeks after IFX treatment, and were also lower in the good response group to IFX. [Conclusions] MMP-3 level was shown to be useful as a disease activity marker of RA patients. In addition, serial measurement of MMP-3 may be helpful to evaluate the effect of treatments with MTX and biologic.

#### W41-5

##### Evaluation of soluble $\alpha$ -Klotho in NPSLE patients

Takeshi Ushigusa<sup>1</sup>, Kunihiro Ichinose<sup>1</sup>, Masataka Umeda<sup>1</sup>, Shoichi Fukui<sup>1</sup>, Ayako Nishino<sup>1</sup>, Yoshikazu Nakashima<sup>1</sup>, Takahisa Suzuki<sup>1</sup>, Yoshiro Horai<sup>1</sup>, Tomohiro Koga<sup>1</sup>, Shin-ya Kawashiri<sup>2</sup>, Naoki Iwamoto<sup>1</sup>, Yasuko Hirai<sup>1</sup>, Mami Tamai<sup>1</sup>, Hideki Nakamura<sup>1</sup>, Tomoki Origuchi<sup>2</sup>, Atsushi Kawakami<sup>1</sup>

<sup>1</sup>Unit of Translational Medicine, Department of Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan, <sup>2</sup>Unit of Rehabilitation Sciences, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan, <sup>3</sup>Department of Public Health, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan

Conflict of interest: None

[Objectives] Klotho is known to play an important role for regulating senescence in central nervous system through calcium homeostasis. However, little is known of significance of serum soluble  $\alpha$ -Klotho (serum Klotho) in neuropsychiatric systemic lupus erythematosus (NPSLE). [Methods] Serum Klotho concentration in NPSLE (N=21), SLE (N=22) and healthy control (HC) (N=46) was measured by ELISA. In each group, statistical associations between serum Klotho and age, sex, disease duration, SLEDAI-2K, anti-dsDNA antibody, anti-Sm antibody, C3, C4 and anti-phospholipid antibody syndrome complication were analyzed. [Results] In comparing NPSLE and SLE, age of onset (median 38 yrs vs. 47.5 yrs:  $p = 0.018$ ) and SLEDAI-2K were statistically significant. Median of serum Klotho concentration in NPSLE (205.3 pg/mL), SLE (297.7 pg/mL) and HC (314.9 pg/mL) were compared. As a result, NPSLE vs HC, and NPSLE vs SLE were statistically significant ( $p < 0.0001$  and  $p = 0.018$ , respectively). Moreover, multivariate analysis showed that lower serum Klotho concentration (Odds ratio (OR), 0.98; 95% confidential interval (CI), 0.96-1.00) or earlier onset of disease (OR, 0.91; 95% CI, 0.81-1.00) would be a risk of NPSLE. [Conclusion] Our findings may indicate the serum Klotho would be a distinguishable marker of NPSLE.

#### W41-6

##### Comparison of test for the new ELISA system and the RNA immunoprecipitation in detection of anti-ARS antibodies

Takeo Abe<sup>1</sup>, Aki Nishioka<sup>1</sup>, Chie Ogita<sup>1</sup>, Yuichi Yokoyama<sup>1</sup>, Tetsuya Furukawa<sup>1</sup>, Takahiro Yoshikawa<sup>1</sup>, Takuya Hino<sup>1</sup>, Atsushi Saito<sup>1</sup>, Naoto Azuma<sup>1</sup>, Masahiro Sekiguchi<sup>1</sup>, Masayasu Kitano<sup>1</sup>, Shinichiro Tsunoda<sup>1</sup>,

Kiyoshi Matsui<sup>1</sup>, Hajime Sano<sup>1</sup>, Yuji Hosono<sup>2</sup>, Koichiro Ohmura<sup>2</sup>, Tsuneyo Mimori<sup>2</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, <sup>2</sup>Rheumatology and Clinical Immunology, Kyoto University Hospital

Conflict of interest: None

[Introduction] Autoantibodies against aminoacyl-tRNA synthetases (ARSs) are the most frequently detected in Polymyositis/Dermatomyositis (PM/DM) patients. And eight types of anti-ARS antibodies have been identified, to date. Each autoantibodies are closely associated with clinical manifestations as interstitial pneumonia, Raynaud's phenomenon, non-erosive arthritis, and mechanic's hands. Currently, the new ELISA system using a mixture of recombinant of anti-ARS antigens: Jo-1, PL-7, PL-12, EJ, KS, is established and covered by insurance. [Objectives] We aimed to assess concordance of the new ELISA system in detection of anti-ARS antibodies, when compared with the RNA immunoprecipitation (RNA-IP). [Methods] Among 45 patients with PM/DM in our institute to whom examined both the RNA-IP and the new ELISA; MESACUP anti ARS test, we evaluated the concordance rate and kappa statistic of the new ELISA. Note that, we removed patients who showed positive titers for anti-Jo-1 antibody ELISA system from this study. [Results] As compared to the RNA-IP, the concordance rate, positive and negative concordance rate of the new ELISA were 95.5 % (43/45), 100% (6/6), and 94.9% (37/39). The kappa statistic was 0.830. [Conclusion] We confirmed this ELISA system is clinically useful as well as RNA immunoprecipitation.

#### W42-1

##### Gene polymorphisms of folylpolyglutamate synthase were determinant factors for intracellular methotrexate in patients with rheumatoid arthritis

Tatsuhiko Yamamoto, Shotaro Masuoka, Mai Kawazoe, Emiko Shindo, Hiroshi Sato, Natsuki Fujio, Kotaro Shikano, Sei Muraoka, Makoto Kaburaki, Nahoko Tanaka, Kaichi Kaneko, Natsuko Kusunoki, Kenji Takagi, Tomoko Hasunuma, Shinichi Kawai  
Division of Rheumatology, Department of Internal Medicine, School of Medicine, Faculty of Medicine, Toho University, Japan

Conflict of interest: None

[Objective] Methotrexate (MTX) is intracellularly converted to polyglutamate compounds (MTXPGs) being active forms by several transporters and enzymes. This study was to investigate the relationship between MTXPGs and gene polymorphisms of solute carrier family 19 member 1, folylpolyglutamate synthase (FPGS), and gamma-glutamyl hydrolase. [Methods] Two hundred and seventy-three patients with rheumatoid arthritis (RA) (Mean $\pm$ SD; 58.3 $\pm$ 9.8 y.o.) undergoing stable oral doses of weekly pulse MTX therapy (8.9 $\pm$ 2.6 mg/week) for at least more than 3 months were included in this study. Individual concentration of MTX-PG<sub>1</sub> to MTXPG<sub>5</sub> in red blood cells were measured by LC-MS/MS method after extraction and purification. The polymerase chain reaction-restriction fragment length polymorphism assay was applied to determine the genotypes. [Results] Mean total concentration of MTXPGs of 273 patients was 108 $\pm$ 12 nmol/L. Mean concentration was dose-dependently increased, however, individual concentration was widely distributed among patients. MTXPG<sub>3-5</sub>/MTXPG<sub>1-2</sub> ratio was significantly increased in patients with gene polymorphisms of FPGS. [Conclusion] FPGS may play an important role in regulation of the intracellular MTXPGs. Measurement of the FPGS polymorphisms may predict clinical responses to MTX therapy.

#### W42-2

##### Correlation of methotrexate efficacy and concentration of erythrocyte methotrexate polyglutamate

Takamasa Murosaki, Takeo Sato, Yoichiro Akiyama, Katsuya Nagatani, Seiji Minota  
Division of Rheumatology and Clinical Immunology, Department of Medicine, Jichi Medical University, Tochigi, Japan

Conflict of interest: None

[Purpose] To clarify the significance of measuring MTX-PG. [Methods] We measured, prospectively, erythrocyte MTX-PG (nM) of 46 patients with rheumatoid arthritis by HPCL from 2013 July to 2014 October, and examined the correlation with the dose and efficacy of MTX. [Results] MTX-PG1, 2, 3 and 1-5 (total of 1 to 5) increased with time after starting MTX. There were correlations between MTX dose and MTX-PG3, 4 (PG3:  $r = 0.541$ ,  $p = 0.006$ ; PG4:  $r = 0.504$ ,  $p = 0.012$ ). At week 24 after initiation of MTX, MTX-PG2, PG1-3, and PG1-5 levels were higher in patients with  $\Delta$ DAS28CRP $>1.2$ , than those with  $\leq 1.2$  (PG2:  $27.7 \pm 10.9$  vs.  $13.8 \pm 4.0$ ,  $p = 0.030$ ; PG1-3:  $91.7 \pm 34.1$  vs.  $49.0 \pm 15.6$ ,  $p = 0.034$ ; PG1-5:  $96.4 \pm 39.0$  vs.  $50.7 \pm 16.9$ ,  $p = 0.044$ ). The cutoff value of MTX-PG1-5 was 68.7 nM. The ratio of patients with  $\Delta$ DAS28 $>1.2$  at week 24 was higher in patients with MTX-PG1-5 $\geq 68.7$  at week 12 than those with  $<68.7$  (week 12: 50.0% vs. 11.1%,  $p = 0.111$ ; week 24: 87.5% vs. 33.3%,  $p = 0.036$ ). [Conclusion] MTX-PG can be a marker of the efficacy of MTX. The correlation between MTX dose and MTX-PG was moderate, indicating that other factors may affect the concentration of MTX-PG.

#### W42-3

##### The retention rate of methotrexate as a first-line DMARDs in elderly rheumatoid arthritis patients

Eigo Kikuchi, Naoto Yokogawa, Naonori Tsuda, Takayasu Kise, Kae Onishi, Yuji Miyoshi, Satoshi Watanuki, Yoshiki Nagai, Takahiro Nunokawa, Toshioki Sawaki, Katsuaki Shiroto, Kota Shimada, Shoji Sugii

Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center

Conflict of interest: None

[Objectives] To analyze the retention rate of methotrexate as a first-line DMARDs in elderly rheumatoid arthritis (RA) patients. [Methods] Data of patients, referred to our department after October 2009, were collected retrospectively from medical records. MTX was started as the first DMARDs treatment (except bucillamine) in 184 RA patients. We divided them into two groups of the elderly groups (65 yo or older) and the young group (others). We analyzed the retention rate of each group by Kaplan-Meier curves. [Results] In the elderly group (64 cases:  $71.0 \pm 4.0$  yo), the average of retention periods was 47.5 months. The cumulative retention rates at 30 and 57 months were 0.812 and 0.774 respectively. In the young group (120 cases:  $48.0 \pm 12.0$  yo), the average of retention periods was 48.0 months. The cumulative retention rates at 30 and 57 months were 0.831 and 0.783. There was no significant difference of the retention rates ( $P=0.87$ ). MTX dose at the end of the observation was  $9.0 \pm 3.3$  mg/w (elderly) and  $9.0 \pm 3.2$  mg/w (young). Steroid usage rate showed 37.5% (elderly) and 19.2% (young) ( $P < 0.01$ ). Biologics combination rates were 7.8% and 24.2% respectively ( $P < 0.01$ ). [Conclusion] Our data suggested that MTX can be used for a long period as a first-line DMARDs for elderly RA patients.

#### W42-4

##### Serum IL-6 level decreased early in proportion to disease activity in patients with rheumatoid arthritis after methotrexate treatment

Masako Tsukamoto<sup>1</sup>, Kunihiro Yamaoka<sup>1</sup>, Keiko Yoshimoto<sup>1</sup>, Noriyuki Seta<sup>2</sup>, Katsuya Suzuki<sup>1</sup>, Tsutomu Takeuchi<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, <sup>2</sup>Department of Internal Medicine, Tokyo Dental College, Ichikawa General Hospital, Chiba, Japan

Conflict of interest: None

[Objectives] We have previously reported that plasma IL-6 level decreased in rheumatoid arthritis (RA) patients with clinically significant improvement after methotrexate (MTX) treatment. We focus on the change of cytokine levels in RA patients treated by MTX at 3 months. The aim of this study is to analyze the relationship between cytokine levels and clinical effectiveness of early MTX treatment. [Methods] 33 RA patients and 15 healthy controls (HC) were enrolled. The patients had moderate disease activity or more and were naïve. Peripheral blood samples and clinical records of the patients were obtained at baseline and following 12 weeks after MTX treatment and serum levels of cytokines

were measured. A decrease in DAS28-ESR $\geq 1.2$  was defined as an improvement after MTX treatment. [Results] Serum levels of IL-6, IL-8 and IL-10 at baseline were significantly higher in RA patients compared with HC, although significant difference was not observed among patients. Serum IL-6 significantly decreased in RA patients with improvement at 12 weeks. However, IL-8 and IL-10 were showed no change. Serum IL-6 level significantly and positively correlated with DAS28-ESR in RA patients at baseline and 12weeks. [Conclusion] Serum level of IL-6 reflects the early effectiveness of MTX treatment.

#### W42-5

##### Usefulness and approval of MIX in Early stage DMARDs naïve RA patients

Shigenori Tamaki<sup>1</sup>, Takashi Kato<sup>2</sup>, Kunikazu Ogawa<sup>3</sup>, Motokazu Kai<sup>3</sup>, Hisaji Oshima<sup>4</sup>, Ikuko Tanaka<sup>1</sup>

<sup>1</sup>Nagoya Rheumatology Clinic, Initiative for Rheumatology and Osteoporosis, <sup>2</sup>Department of Radiology, National Center for Geriatrics and Gerontology, Obu, Japan, <sup>3</sup>Mie Rheumatology Clinic, Initiative for Rheumatology and Osteoporosis, Suzuka, Japan, <sup>4</sup>Department of Connective Tissue Disease, Tokyo Medical Center, National Hospital Organization, Tokyo, Japan

Conflict of interest: None

[Objectives] We examined usefulness and approval of MTX for DMARDs naïve early RA patients. [Methods] 121 early RA patients were started MTX medication with 8mg/w. MTX was increased in order that the patients reach to Boolean remission or doppler remission. [Results] The rate of the patients for the maximal dosage for 52weeks and the dosage at 52week were 39% and 29% for 16mg, and 82% and 67% for more than 10mg. MTX was reduced in 26% of the patients, in two thirds of who presented hyper ALT-emia. MTX was reduced in 0%, 13% and 17% of the patients who were medicated with the dose of 8mg, 12mg and 16mg respectively. The remission rates at each dosage were 24% at 8mg, 47% at the less than 12mg, and 72% at the less than 16mg. 13 patients were medicated with 16 mg and MTX dose was not reduced for 104 weeks. The serum ALT (IU/L) levels of these patients were  $15 \pm 10$  at the baseline,  $32 \pm 23$  at 32week (significant increase),  $46 \pm 32$  at 68week (increasing in time-course), and around 20 after 84week (dropped to the level of no significant increase from the baseline). [Conclusion] Increased dosage of MTX is effective for the remission of RA. Re-increase of dosage of MTX should be considered after the reduction, as hepatic function affected by MTX can be recovered even in continuing MTX therapy.

#### W42-6

##### The annual hospitalization number for serious adverse events for high dose MTX monotherapy in Japanese patients with RA using NinJa 2013 cohort

Atsushi Kaneko<sup>1,4</sup>, Toshihiro Matsui<sup>2,4</sup>, Daihei Kida<sup>1</sup>, Yosuke Hattori<sup>1</sup>, Hiroyasu Kanda<sup>1</sup>, Shigeto Tohma<sup>3,4</sup>

<sup>1</sup>Dept. of Orthop. Surg. And Rheumatology, Nagoya Medical Center, National Hospital Organization, <sup>2</sup>Department of Rheumatology, Sagamiara National Hospital, Kanagawa, Japan, <sup>3</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamiara National Hospital, NHO, Kanagawa, Japan, <sup>4</sup>iR-net

Conflict of interest: None

[Objectives] The purpose of this present study is to review serious adverse event by MTX dose dependent in patients with RA. [Methods] In 13285 Japanese RA patients registered with NinJa2013, 4227 patients medicated MTX monotherapy without biological DMARDs and combination synthetic DMARDs were divided 5 groups by MTX dose once a weekly.; 1-4mg/week n=563 average age 68.6years old, mean duration of illness 14.3years, 5-7mg/week n=993, 64.5years old, 11.2years, 7.5-8.5mg/week n=1149, 63.1years old, 11.2years, 9-11mg/week n=729: 60.8years old, 10.7years, over 12mg/week n=746: 56.7years old, 8.8years, respectively. We defined hospitalization for various infectious disease (including opportunistic infections), interstitial pulmonary disease, pancytopenia, malignant lymphoma as serious adverse event and research annual hospitalization. Final, we compare the event number for 5 groups by Odds ratio. [Results] The annual hospitalization number

were 18 patients in 1-4mg/week group, 22 patients in 5-7mg/week group, 17 patients in 7.5-8.5mg/week group, 9 patients in 9-11mg/week group, 11 patients in over 12mg/week group. Incidence of serious adverse event of the all NinJa 2013 cohort was 463 patients (3.5%), and the OR with each group were 0.91, 0.83, 0.42, 0.35, 0.42 respectively.

#### W43-1

##### **The effectiveness and adverse effects of rituximab therapy for severe form of MPO-ANCA-associated vasculitis (MPO-AAV)**

Yoshihisa Nomura<sup>1</sup>, Yuriko Yamamura<sup>2</sup>, Kazuyuki Fujita<sup>2</sup>, Akiko Ueno<sup>2</sup>, Shinsuke Nishimura<sup>1</sup>, Noriyo Momoki<sup>1</sup>, Keisuke Maruyama<sup>1</sup>, Tsuneto Onbe<sup>1</sup>, Masahiro Yamamura<sup>2</sup>

<sup>1</sup>Center for Kidney Diseases, Okayama Saiseikai General Hospital, Okayama, Japan, <sup>2</sup>Center for Rheumatology, Okayama Saiseikai General Hospital, Okayama, Japan

Conflict of interest: None

[Objectives] To determine the effectiveness and adverse effects of rituximab (RTX) therapy for severe form of MPO-ANCA-associated vasculitis (MPO-AAV). [Methods] We had started the RTX therapy for 3 patients with microscopic polyangiitis (MPA) and a patient with granulomatosis with polyangiitis (GPA), and their therapeutic responses and adverse effects have been monitored. [Results] All four patients had shown rapidly progressive glomerulonephritis (RPGN) and pulmonary involvement, e.g. interstitial pneumonia, alveolar hemorrhage, organizing pneumonia, and granuloma, thus all classified as severe forms of AAV. They were most successfully treated with corticosteroids and RTX, but three patients experienced cytomegalovirus (CMV) reactivation, of whom one suffered from CMV enteritis. [Conclusion] The results suggest that RTX is effective for patients with severe MPO-AAV, but CMV reactivation should be monitored.

#### W43-2

##### **A study of the effects of rituximab therapy for refractory ANCA-associated vasculitis in spite of the conventional treatment**

Shinichiro Tsunoda, Kota Azuma, Takeo Abe, Chie Ogita, Yuichi Yokoyama, Takuya Hino, Masahiro Sekiguchi, Naoto Azuma, Masayasu Kitano, Kiyoshi Matsui, Hajime Sano

Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine

Conflict of interest: None

[Objectives] We examined the therapeutic effect of rituximab for relapsed ANCA-associated vasculitis in our department. [Background of patients] Relapse 8 cases (male 1, female 7, 66±18 years old, disease duration 65.5±52.8 months). 7 cases were diagnosed as Granulomatosis with Polyangiitis (GPA), and one case was diagnosed as Microscopic Polyangiitis (MPA). Four cases MPO-ANCA was high, and four cases PR3-ANCA was high at the onset of the disease. Four cases ANCA was high before rituximab therapy and two cases ANCA was still high after rituximab therapy. [Results] All patients improved the pain and other symptom of ANCA-associated disease and we could reduce the dose of the prednisolone. One case developed a fungal pneumonia and brain abscess. [Conclusion] Rituximab could be the key drug of the ANCA-associated vasculitis.

#### W43-3

##### **B cell abnormality and efficacy of rituximab in patients with ANCA associated vasculitis**

Shingo Nakayamada, Maiko Yoshikawa, Yuichi Ishikawa, Yusuke Miyazaki, Kazuhisa Nakano, Satoshi Kubo, Ipppei Miyagawa, Shunsuke Fukuyo, Akio Kawabe, Aya Nawata, Hiroko Yoshinari, Masahiro Saito, Kazuyoshi Saito, Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health

Conflict of interest: None

[Objectives] B cell depletion by rituximab is effective treatment for

ANCA associated vasculitis (AAV). However, the selection criteria for RTX remain unclear. [Methods] Circulating B cell subsets were defined by flow cytometry in 11 AAV patients (4 GPA, 6 MPA, and 1 EGPA). Based on the analysis, the patients were considered suitable to receive immunosuppressive drugs or RTX. [Results] All patients had organ involvements including upper and lower respiratory tract or nephropathy, and were treated with high dose steroids. The proportion of effector memory or class-switched memory B cells was increased in 5 patients, thereby treated with RTX (375mg/m<sup>2</sup> once per week for four times) and all achieved in clinical improvement. Six patients without B cell abnormality received immunosuppressants (3 IVCY and 3 azathioprine): 4 patients achieved clinical improvement, but two patients died from alveolar hemorrhage and severe infection. [Conclusion] The results suggested that RTX therapy is effective in AAV patients with abnormal B cell differentiation to effector memory B cells. The evaluation of B cell phenotype may serve to predict to the response to RTX therapy in AAV.

#### W43-4

##### **Efficacy of rituximab in 13 cases with ANCA-associated vasculitis**

Hisae Ohjimi, Hiromi Matsushita, Teisuke Uchida, Hirofumi Mitomi, Hiroshi Ito, Yoshioki Yamasaki, Seido Ooka, Takahiro Okazaki, Hidehiro Yamada, Shoichi Ozaki

Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

Conflict of interest: None

Objective: To retrospectively evaluate the efficacy, safety and tolerability of induction therapy with rituximab for ANCA-associated vasculitis from 2006 to 2014. Cases: There were 13 cases (6 male and 7 female). Mean age was 51.3. They were classified with granulomatosis with polyangiitis (10 cases), microscopic polyangiitis (2), and eosinophilic granulomatosis with polyangiitis (1). 10 cases were PR3-ANCA positive, 3 cases were MPO-ANCA positive. Seven cases were cyclophosphamide (CY)-resistant and 6 cases were CY-naïve. The life-threatening organ involvement included 3 retrobulbar granuloma, 2 tracheal stenosis, 11 pulmonary diseases, and 4 necrotizing crescentic nephritis. Average of BVAS was 14.8 at the administration of rituximab. Rituximab at a dose of 375 mg per square meter of body-surface area weekly was administered for 4 weeks. Average of initial prednisolone (PSL) dose was 38.8mg/day. Concomitant methotrexate and azathioprine were added in 2 and 3 cases, respectively. Remission was induced within 24 weeks in all cases. The PSL was reduced to an average of 9.3 mg/day. Three minor adverse events such as fever, cutaneous pruritus and upper respiratory tract infection were observed. Conclusion: Rituximab was effective and safe in our cohort of ANCA-associated vasculitis.

#### W43-5

##### **A case report of hypertrophic cranial pachymeningitis in EGPA which responded well to Rituximab**

Hiroki Furuya, Kotaro Kumano, Masaki Hiraguri, Takao Yanagisawa  
Japanese Redcross Narita Hospital

Conflict of interest: None

A 40 year old woman with past medical history of asthma and eosinophilic pneumonia arrived to hospital complaining of stomachache on 20XX, November. She had leukocytosis with 42% of eosinophil and was treated with PSL 20mg as eosinophilic gastroenteritis. On March next year, she developed polymyoneuropathy and was MPO-ANCA positive, which led to diagnosis of EGPA. Two courses of dexamethasone pulse therapy and IVIG relieved only her stomachache. The mononeuropathic pain worsened and her stomachache, eosinophilia and inflammation continued on recurring. The use of betamethasone, azathioprine, cyclophosphamide, tacrolimus and IVIG could not relieve her. On July, she readmitted due to worsening headache, fever, nausea, dysgeusia and polyopia. Cerebrospinal fluid IL-6 was 173 pg/ml and contrast-enhanced MRI showed hypertrophic cranial pachymeningitis. As the treatment listed above did not improve her condition before, rituximab was administered in addition to the extra betamethasone dosage. Her dysgeusia and polyopia responded well and was able to discharge soon. Hypertrophic cranial pachymeningitis is often reported to be the complication of GPA, while

our case was complicated with EGPA, and showed good response to rituximab. We report this rare case with some literature review.

#### W43-6

##### **Tocilizumab achieved lasting remission of granulomatosis with polyangiitis for more than two years**

Mamoru Inoue<sup>1,2</sup>, Yutaka Kawahito<sup>3</sup>

<sup>1</sup>Department of Laboratory, Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan, <sup>2</sup>Department of Metabolism, Nephrology and Rheumatology, Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan, <sup>3</sup>Department of Inflammation & Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: None

Granulomatosis with polyangiitis (GPA) is, one of ANCA-associated vasculitis (AAV), liable to recurrence. Effectiveness of tocilizumab (TCZ) for the treatment of AAV is increasingly reported in recent days. This time we report, with bibliographic considerations, one case of GPA recurred with visual disturbance which was achieved lasting remission by the therapy of prednisolone (PSL) with TCZ for more than 2 years and withdrew from PSL. A 70-year-old female developed with fever, weight loss, rhinorrhea and severe bilateral hearing loss four years ago. She achieved a remission once by combination therapy of PSL, cyclophosphamide (CPA), and sulfamethoxazole-trimethoprim. A half year later, she had a relapse and treated with increasing dose of CPA. She achieved a remission again, but came off it for bone-marrow suppression. Then, she kept lull with only PSL therapy for 9 months, but had relapse again with right optic disc edema and visual disturbance. Increasing dose of PSL with some immunosuppressive was ineffective, but drip infusion of TCZ ameliorated her condition. She achieved remission again, and then the TCZ therapy was switched to subcutaneous injection. Finally, she withdrew from PSL after 2 years from the start of TCZ. We experienced an effective case of GPA with TCZ.

#### W44-1

##### **Clinical characteristics and prognosis in of patients with ANCA-associated vasculitis for the past five years.: results from a single university center**

Chinatsu Takai<sup>1</sup>, Yoko Wada<sup>1</sup>, Ayako Wakamatsu<sup>1</sup>, Yukiko Nozawa<sup>1</sup>, Hiroe Sato<sup>1</sup>, Takeshi Nakatsue<sup>1</sup>, Takeshi Kuroda<sup>2</sup>, Masaaki Nakano<sup>3</sup>, Ichiei Narita<sup>1</sup>

<sup>1</sup>Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, <sup>2</sup>Health Administration Center, Niigata University, <sup>3</sup>School of Health Sciences, Faculty of Medicine, Niigata University

Conflict of interest: None

[Objectives] To examine the recent characteristic features in patients with ANCA-associated vasculitis (AAV). [Methods] Forty patients (20 males and 20 females, mean age at onset 68±10) who had been referred to Niigata University Hospital and diagnosed as AAV between 2009 and April 2014, were recruited. The patients' data were collected from their clinical records. [Results] Twenty-one patients were diagnosed as microscopic polyangiitis (MPA), 17 as granulomatosis with polyangiitis (GPA), and 2 as eosinophilic granulomatosis with polyangiitis (EGPA). There was a trend for increasing in number of patients with AAV, especially those with GPA. Three patients died, and 4 underwent hemodialysis during follow-up period. All patients were positive for MPO-ANCA in MPA, while 10 were positive for MPO-ANCA and 6 were positive for PR3-ANCA in patients with GPA. Although interstitial pneumonia and autoimmune disorders were common complications and renal function was significantly deteriorated at the onset in patients with MPA, hearing impairment was the major complication in those with GPA. Relapse rate was higher in GPA, and the association of infection was commonly observed in MPA. [Conclusion] The numbers of AAV patients, especially MPO-ANCA-positive GPA, was increasing in our study.

#### W44-2

##### **Clinical Study of Anti-neutrophil Cytoplasmic Antibody-associated Vasculitis (AAV) with a Focus on Microscopic Polyangiitis (MPA)**

Konomi Ashihara, Shusaku Fukaya, Soichi Yamada, Akiko Yoshida, Daisuke Hirano, Satoru Onoda, Jo Nishino, Kenichi Kato, Shunji Yoshida  
Section of Rheumatology and Infectious Diseases, Department of Internal Medicine, School of Medicine, Fujita Health University, Toyoake, Japan

Conflict of interest: None

**Objective** The objectives of this study were to clinically characterize AAV with a focus on MPA and to investigate the effects these diseases have on treatment and disease outcomes. **Subjects and Methods** A total of 47 patients with MPA, granulomatosis with polyangiitis (GPA), or eosinophilic granulomatosis with polyangiitis (EGPA) hospitalized in our department during the past 5 years was retrospectively investigated. **Results** All 47 patients received steroid treatment. Intermittent intravenous cyclophosphamide (IVCY) was administered to the lung, kidney, and nerve lesions in patients with MPA. The IVCY target lesions in the lungs were all pulmonary alveolar hemorrhage. The 50-month survival of AAV was 100% for GPA, 89% for EGPA, and 83% for MPA. In MPA, six patients died during the follow up period. Five of them died due to infections, primarily of the lungs. **Discussion and Conclusions** In MPA patients, lung involvement was not a target lesion for strong immunosuppressant therapy. But since lung infections are often the cause of death of MPA patients, lung lesions may influence poorer prognosis.

#### W44-3

##### **The long-term survival predictors of the microscopic polyangiitis patients in our Center**

Yoshiyuki Abe<sup>1</sup>, Kwangseok Yang<sup>2</sup>, Jun Suzuki<sup>2</sup>, Takayuki Kon<sup>1</sup>, Ken Yamaji<sup>1</sup>, Naoto Tamura<sup>1</sup>, Hiroshi Tsuda<sup>2</sup>, Yoshinari Takasaki<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Juntendo University, Tokyo, Japan, <sup>2</sup>Juntendo Tokyo Koto Geriatric Medical Center, Tokyo, Japan, <sup>3</sup>Juntendo Clinical Research Support Center, Tokyo, Japan

Conflict of interest: None

[objectives] we examined the long-term survival predictors of the microscopic polyangiitis patients who has been hospitalized in our Center. [methods] For 50 microscopic polyangiitis patients that we applied European Medicines Agency algorithm among 70 ANCA associated vasculitis patients that have been hospitalized from 2002 through 2014 in our Center. We examined the long-term survival predictors. [results] The mean follow-up period was 25.4±28.1 months. 28 patients were confirmed dead, and were 50.4±8.6 month for mean survival time. We performed a multivariate analysis with five factors ages, severity, corticosteroid dosage per body weight (CS/BW), combination therapy with immunosuppressant and with prophylaxis agents of PCP. Assumed that primary outcome was all-cause mortality, three factors ages, severity and CS/BW were significant risk factor. Therefore, the prophylaxis of PCP was significant prognosis-improving factor. These factors were not related to infection death and significantly related to vasculitis death. [conclusion] Even if it was an elderly person in particular, it was expected without being afraid of infection death to a patient of the high disease activity whether appropriate extreme treatment should intervene.

#### W44-4

##### **Efficacy and safety of remission-induction/maintenance therapy in ANCA-associated vasculitis; A single center case series study**

Yuichiro Ota, Takahiko Kurasawa, Katsuya Suzuki, Tsutomu Takeuchi  
Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] Aim of this study is to reveal current status of ANCA-associated vasculitis (AAV) treatment. [Methods] Clinically diagnosed AAV cases admitted to our Rheumatology service from January 2012 until September 2014 were enrolled. Clinical information was collected from medical chart and statistically analyzed. [Results] Thirty AAV cases

including 22 new-onset (MPA/GPA/EGPA: 8/7/7, average age 65.8±13.1 years old) and 8 relapse (MPA/GPA: 4/4) cases were evaluated. Clinical manifestations were various, fever (14), skin lesions (3), neurological (8), upper airway lesions (14), lung (17), and renal involvements (9). In remission-induction treatment, average amounts of glucocorticoids (GC) were 0.86 mg/kg/day as prednisolone. Immunosuppressants (IS) were used for 22 cases (IVCY 14, AZP 6, MTX 1, MMF 1). Rituximab were used in 4 cases for induction and 3 for maintenance. Remission achievement rate was very high and relapse was found in 3 cases. Total 22 cases had adverse events (Infection 15, dyslipidemia 8, hypertension 6, and diabetes mellitus 4). Only one died in infection. [Conclusion] Although remission-induction therapy by GC and IS was largely effective in AAV, further optimization of treatment strategy for less adverse events including infection is needed.

#### W44-5

##### Analysis of clinical features over 30 years in ANCA associated vasculitis

Soko Kawashima, Ken Yoshihara, Yoshinori Komagata, Shinya Kaname, Yoshihiro Arimura

First Department of Internal Medicine, Kyorin University School of Medicine

Conflict of interest: None

[Objectives] ANCA-associated vasculitis (AAV) is a systemic inflammatory disease characterized by necrotizing vasculitis. Recently, early detection and treatment has improved the prognosis. Therefore, we analyzed the clinical problems of AAV by using the date of the past 30 years. [Methods] 185 patients with AAV (69 male and 116 female) who were admitted to our hospital after 1983 were followed up. We divided into three groups (Group I: 1983~1998, Group II: 1999~2002, Group III: 2003~) and analyzed the clinical features. [Results] 1) The average age of onset were 64.4 (Group I), 63.2 (Group II) and 71.2 (Group III) years old. 2) BVAS (Birmingham Vasculitis Activity Score) were 24.4 (Group I), 21.1 (Group II) and 17.3 (Group III). 3) Serum creatinine were 5.8mg/dl (Group I), 3.3mg/dl (Group II) and 2.5mg/dl (Group III). 4) One year survival rate were 60% (Group I), 80% (Group II) and 80% (Group III). [Conclusion] Recently, early detection and early treatment have enabled therapeutic intervention in the early stage and have improved the prognosis. However, more than 60% of AAV onset is over 70 years. We should consider comprehensive treatments for elderly patients.

#### W44-6

##### Comparison of malignant rheumatoid arthritis in Japan and Western countries in the era of biologics

Takeshi Zoshima, Kazunori Yamada, Shigeto Horita, Hiromi Nuka, Satoshi Hara, Kiyooki Ito, Motohiko Aizu, Hiroshi Fujii, Mitsuhiro Kawano

Division of Rheumatology, Kanazawa University Hospital

Conflict of interest: None

Objectives; Rheumatoid arthritis (RA) with vasculitis is called malignant RA (MRA) in Japan, and rheumatoid vasculitis (RV) in Western countries. We investigated their characters in the era of biologics (BIO). Methods; We enrolled 15 Japanese MRA patients (pts) (8 women; mean age 62.3 years at MRA; observation period 3.9 years) diagnosed at our hospital from 2000 to 2013. We analyzed retrospectively clinical findings, treatment and prognosis. We compared MRA pts with RV ones, diagnosed in almost the same period in UK (18 pts) and USA (86 pts) reported in 2014 respectively. All pts met the Scott and Bacon criteria (1984). Results; In MRA, cutaneous lesion (73%), lung one (40%), and neuropathy (20%) were common. Histopathological confirmation was available for 60%. BIO-induced vasculitis was suspected in one pts. Treatment for RA before MRA was PSL (80%), MTX (27%), BIO (13%), and others. After development of MRA, PSL (93%) and BIO (53%) were common. Severe infection developed in 33% with 2 pts dead. Compared with RV, MRA had higher frequency of hypocomplementemia (HL) (67% vs 14%) and lower one of ANCA positivity (0% vs 37%). Lower frequency of CPA use in MRA led no difference in mortality. Conclusions; HL can be a useful marker for diagnosis and follow up of MRA rather

than RV.

#### W45-1

##### Association of physical/daily activity functions with muscle strength at lower limb joints

Shinichiro Fujita<sup>1</sup>, Yoshihisa Nasu<sup>2</sup>, Wataru Yamamoto<sup>3</sup>, Tomohiro Yoshida<sup>1</sup>, Masamitsu Natsumeda<sup>4</sup>, Koji Takasugi<sup>4</sup>, Misuzu Yamashita<sup>4</sup>, Kazuhiko Ezawa<sup>4</sup>, Keiichiro Nishida<sup>5</sup>

<sup>1</sup>Department of Rehabilitation, Kurashiki Sweet Hospital, Kurashiki, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Center of Rheumatology, Kurashiki Sweet Hospital, Kurashiki, Japan, <sup>3</sup>Department of Clinical Information Management, Kurashiki Sweet Hospital, Kurashiki, Japan, <sup>4</sup>Department of Internal Medicine, Center of Rheumatology, Kurashiki Sweet Hospital, Kurashiki, Japan, <sup>5</sup>Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Conflict of interest: None

[Objectives] We previously reported that progression of lower limb dysfunction is not associated with disease activities in RA patients treated with biologic DMARDs. Therefore, aim of our study is to investigate association of physical/daily activity function with muscle strength at lower limb joints. [Method] 121 RA patients treated with biologics were separated based on muscle strength assessed by Manual Muscle Testing (MMT) values (normal MMT vs reduced MMT) at each joints of crotch, knees, and legs. Walking ability (10-m walking rate) and balancing ability (Functional Reach Test (FRT)/Timed Up and Go test (TUG)), and ADL ability (Functional independence) at both groups were assessed for any differences ( $p < 0.05$ ). [Result] There was a significant difference between normal MMT and reduced MMT in FRT at knees as well as walking ability and TUG at ankle bottom flexor and hip joint extension muscles. FIM showed significant differences at ankle bottom flexor, hip joint extension muscles, and knee joint extension muscles. [Consideration] Generally, kinematic strategy focuses on ankle joint for young and on hip joint for ageing people. However, our result showed RA patients who have functional disabilities at many joints have different pattern from normal population.

#### W45-2

##### Study of music therapy for general self-efficacy of patients with rheumatoid arthritis by using the Self-Efficacy Scale

Yasushi Miura<sup>1,2</sup>, Ikuko Yamazaki<sup>3</sup>, Kenya Oga<sup>3,4</sup>, Toshihisa Maeda<sup>2</sup>, Koji Fukuda<sup>5</sup>, Masahiro Kurosaka<sup>2</sup>

<sup>1</sup>Dept. of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Japan, <sup>2</sup>Dept. of Orthopaedic Surgery, Kobe University Graduate School of Med., Kobe, Japan, <sup>3</sup>Dept. of Healthcare and Welfare, International University of Health and Welfare, Tokyo, Japan, <sup>4</sup>Yokote Kohsei Hospital, <sup>5</sup>Dept. of Orthopaedic Surgery, Kakogawa City Hospital, Kakogawa, Japan

Conflict of interest: Yes

[Objectives] We previously reported that music therapy improves general health condition, pain, and anxiety of patients with rheumatoid arthritis (RA) attending to the patient class. In this study we investigated the effect of music therapy for the self-efficacy of patients with RA. [Methods] Music therapy was conducted by a music therapist, a pianist, hospital staffs, and healthcare students. Eight Japanese songs were sung with a piano accompaniment and 2 were played with chime bars (a sort of hand bells) by the participants. General health condition, pain, state anxiety, and general self-efficacy were surveyed by self-rating questionnaire including 10cm VAS, face pain rating scale, and the Self-Efficacy Scale. [Results] Nineteen patients with RA (18 females and 1 male) participated. mHAQ of the attendee was 0.57±0.80. VAS was improved from 3.4±2.5 to 2.8±2.5, and both face scale and SES were improved significantly from 7.3±4.1 to 3.9±3.1 ( $P < 0.01$ ) and 68.2±9.9 to 72.0±11.3 ( $P < 0.05$ ) respectively by music therapy. [Conclusion] Music therapy improves general health condition, pain, anxiety, and self-efficacy of patients with RA.



### W45-3

#### Assessment for the functional therapy with custom foot orthoses for rheumatoid arthritis

Shogo Toyama<sup>1,2</sup>, Ryo Oda<sup>2</sup>, Daigo Taniguchi<sup>2</sup>, Heidai Mitsumoto<sup>3</sup>, Daisaku Tokunaga<sup>2</sup>, Masahiko Shibata<sup>1</sup>, Kazuya Ikoma<sup>2</sup>, Hiroyoshi Fujiwara<sup>2</sup>, Toshikazu Kubo<sup>2</sup>

<sup>1</sup>Department of Orthopedics, Japan Community Health Care Organization Kobe Central Hospital, Kobe, Japan, <sup>2</sup>Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, <sup>3</sup>Department of Rehabilitation, Japan Community Health Care Organization Kobe Central Hospital, Kobe, Japan

Conflict of interest: None

[Objective] Though foot orthoses are reported to be effective to the foot lesion in rheumatoid arthritis (RA), they have some problems including low adherence. Producing perfectly matched orthoses at once is a difficult work. We conduct 3-month functional therapy with custom-made orthosis. In this study, we assessed the effectiveness of the orthosis. [Methods] Fourteen RA patients (1 male, 13 females) who have complaints in the foot were involved in this study. The average age was 68.8 years and the average affected period was 105.8 months. The resistance muscle training, endurance training and gait training were performed. We assessed pain scale, muscle strength, gait speed and QOL scores. [Results] No patients sustained the therapy due to the mismatch of orthoses. Muscle output increased significantly, gait speed improved by 9.9% on barefoot and improved by 18.3% with orthoses. Pain decreased from 13.3mm to 4.0mm in visual analogue scale. SF-36 improved especially in "physical QOL" and "mental QOL" field. [Conclusion] However well-matched orthoses are necessary for the effective physical therapy, the problems of low adherence still exists. In this study, gait disturbance and QOL made improvement. Our custom made orthoses are effective to resolve the adherence.

### W45-4

#### Foot care of the patients with rheumatoid arthritis

Kiyoshi Nakazono, Akira Murasawa, Hajime Ishikawa, Satoshi Ito, Asami Abe, Hiroshi Otani, Daisuke Kobayashi, Tomo Oyakawa, Kengo Harigane, Satoru Kodama  
Niigata Rheumatic Center, Shibata, Japan

Conflict of interest: None

[Objectives] We evaluated the foot care that we performed in our hospital. [Methods] 149 RA patients (male:female 10:139, average 64.4 years old) who performed foot care during going to hospital in our hospital from April, 2014 to September. As for the measures of the foot care, callosity debridements, corn debridements and the measures of the nail were enforced. We evaluated the foot pain in before and after foot care with VAS. [Results] Callosity debridements (119), corn debridements (49), nail measures (19) were enforced. VAS of the foot pain in before and after foot care was seen in 4 immutability, aggravation 2, improvement 143. [Conclusion] The satisfaction by the foot care is good, but it seems that care of the reduction of the recurrence of the callus such as shoes or the insole would be necessary in future.

### W45-5

#### Effect of range of motion (ROM) exercise of MTP joints after shortening osteotomy for RA forefoot deformities

Naotaka Tazaki<sup>1</sup>, Hideki Tsuboi<sup>2</sup>, Kouhei Kushimoto<sup>1</sup>, Shosuke Akita<sup>3</sup>, Yukihiko Saeki<sup>4</sup>, Jun Hashimoto<sup>2</sup>

<sup>1</sup>Department of Rehabilitation, National Hospital Organization Kyoto Medical Center, Kyoto, Japan, <sup>2</sup>Department of Rheumatology, National Hospital Organization Osaka Minami Medical Center, <sup>3</sup>Department of Orthopedics, National Hospital Organization Osaka Minami Medical Center, <sup>4</sup>Department of Clinical Research, National Hospital Organization Osaka Minami Medical Center

Conflict of interest: None

[Objectives] To verify the effect of passive ROM exercise for MTP joint after offset shortening osteotomies for RA lesser toe deformities us-

ing a motion analyzer system during walking intervals. [Method] 18 RA patients were enrolled in this study. 9 patients were performed passive ROM exercise (group; ROMex) and 9 were not performed (group; non ROMex) and 4 healthy volunteers without forefoot deformities were enrolled (group; Control). All patients had the same operation on the lesser toes using an offset shortening osteotomy of metatarsal bones. We assessed ROM of MTP joints and JSSF (lesser toe) scale after the operation in those two operated groups respectively. Moreover, we measured the angle of MTP joints of lesser toes on the terminal stance phase of the affected limb during walking intervals using a motion analyzer. [Result] The results from a motion analyzer system showed that the average angle of MTP joints extension were 22.3±7.3°/ 11.9±6.3° in the group of ROMex / non ROMex, respectively, on the other hand, the extension in the Control was 31.9±9.5°. JSSF score were 85.6±7.9 / 78.4±10.4 in ROMex / non ROMex, respectively. [Conclusion] This study suggests that passive ROM exercise is useful after an operation on the forefoot in RA patients.

### W45-6

#### A case report: two patients with rheumatoid arthritis enabled to manage foot self-care by occupational therapy intervention

Kinue Matsuo<sup>1,2</sup>, Emi Motoki<sup>3</sup>, Yasuhiro Terashima<sup>4</sup>, Natsuko Nakagawa<sup>4</sup>, Yasushi Miura<sup>2</sup>

<sup>1</sup>Department of Rehabilitation, Konan Kakogawa Hospital, Kakogawa, Japan, <sup>2</sup>Department of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Japan, <sup>3</sup>Graduate School of Nursing Art and Science, University of Hyogo, Akashi, Japan, <sup>4</sup>Department of Orthopaedic Surgery, Konan Kakogawa Hospital, Kakogawa, Japan

Conflict of interest: None

[Background] To keep foot hygiene is difficult for patients with rheumatoid arthritis (RA) because of toe deformities or limited range of motion (ROM) of upper and lower extremities. Here we report 2 patients with RA enabled to manage foot self-care by occupational therapy intervention. [Case1] A 71-year-old female. Active extension ROM of the right elbow was decreased to -60°. In December 2010, a total knee arthroplasty was performed on the left. Her skin condition of feet was poor because her hands could not reach the feet or press a container for moisturizer. We offered self-help devices to apply moisturizer and press a container. [Case2] A 56-year-old female. In June 2013, a total hip arthroplasty was performed on the right. Her both hands could not reach the forefeet. The skin between toes was macerated and her skin condition of feet was poor. We offered a self-help device to apply moisturizer and a long handle interdental brush. [Results] They were enabled to perform appropriate foot self-care including skin moisturization and keep foot hygiene. [Discussion] Foot care is one of the frequently-overlooked activities of daily living for patients with RA. An occupational therapist is expected to support patients for appropriate foot self-care including offer of self-help devices.

### W46-1

#### The efficacy of Pregabalin for Fibromyalgia treatment in our hospital

Hisamune Kato  
Mimihara Otori Clinic

Conflict of interest: None

[Objectives] This study aimed to evaluate the efficacy of Pregabalin for Fibromyalgia treatment. Eight patients who visited our hospital complaining of widespread pain and were made diagnosis of Fibromyalgia were enrolled. [Methods] The diagnosis of Fibromyalgia was made on the basis of the 1990 ACR Diagnostic Criteria for Fibromyalgia. All of the patients took Pregabalin. Patients with PtGA<5mm using the VAS were considered to be under good control. [Results] Pregabalin was considered to be effective in only 3 patients (37.5%). 3 patients discontinued Pregabalin because of side effects. 1 patient discontinued because of inefficacy. 1 patient discontinued because of unknown reason. It is of interest that treatment with Duloxetine plus small dose of Pramipexole was considered to be effective in one patient who failed in treatment with Pregabalin or Duloxetine monotherapy. [Conclusion] Main reason of dis-

continuation of Pregabalin was considered to be side effects. All of the patients who continued Pregabalin were under good control. We might recognize the efficacy of Pregabalin. In institution of treatment with Pregabalin, prevention of side effects might be important. Furthermore addition of small dose of Pramipexole might be effective.

#### W46-2

##### Open label randomized controlled trials with bosentan and tadalafil for Raynaud's phenomenon complicated with CTD-PAH patients

Keisuke Hagihara<sup>1</sup>, Yuki Kishida<sup>1</sup>, Miho Nakanishi<sup>1</sup>, Hideki Yoshikawa<sup>2</sup>  
<sup>1</sup>Department of Kampo Medicine, Osaka University Graduate School of Medicine, Osaka, Japan, <sup>2</sup>Department of Orthopedic Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

Conflict of interest: Yes

[Objectives] We performed randomized controlled trials of bosentan and tadalafil for Raynaud's phenomenon complicated with CTD-PAH patient to investigate an effective therapeutic strategy. [Methods] 17 patients were registered (F: M = 14: 3, 59.0 ± 15.0 years of age, BMI 19.5 ± 5.6, SSc 8, SLE 5, MCTD1, RA 1, SjS 1, DM 1). 9 cases of bosentan group (B group) and 8 cases of tadalafil group (T group) were allocated using a permuted block method randomization. The cold immersion test was performed to evaluate Raynaud's phenomenon using thermography before and 3 months after treatment. At the same time SF-36v2 questionnaire and cardiovascular test were carried out. [Results] The clinical background of patients were as follows; the mean dosage of PSL 3.8 ± 4.2mg, biologics 2, FK506 1, WHO class II 17, Borg score 3.13 ± 1.67, BNP 34.4 ± 33.0pg / ml, 6-MWT 419.0 ± 51.5m, and TRPG 23.3 ± 5.5 mmHg. Both group of the left hand temperature were significantly improved (B group: 30.1 ± 1.86 °C → 32.9 ± 0.95 (p=0.0026, paired-t), T group: 29.8 ± 1.74 °C → 33.2 ± 0.74 (p=0.0007). The QOL score significantly improved in the B group. Borg score and TRPG significantly decreased in the T group. [Conclusion] Both drug showed the same effect on Raynaud's phenomenon, but the mechanism of the efficacy were different.

#### W46-3

##### Calcium pyrophosphate deposition disease presenting as "vertebral pseudo-osteomyelitis"

Yuji Miyoshi, Eigo Kikuchi, Toshioki Sawaki, Takahiro Nunokawa, Yoshiki Nagai, Satoshi Watanuki, Takayasu Kise, Kae Onishi, Naoto Yokogawa, Kota Shimada, Shoji Sugii  
Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan

Conflict of interest: None

In the elderly, CPPD deposition disease can mimic clinical conditions including gout, RA and PMR. The reports of clinical axial skeletal CPPD deposition diseases at vertebral body and intervertebral disks are scarce. We report 2 cases of vertebral osteomyelitis accompanying CPPD induced polyarthritis. [Case1] A 66-year-old man was admitted for acute onset of high fever, severe pain on neck, and polyarthritis of wrists, knees and ankles. Arthrocentesis of the wrists and knees yielded inflammatory joint fluid and microscopic examination of the fluid revealed CPPD crystals. MRI of the spine showed enhancement at the C6 and C7 vertebral bodies and the disk space. Treatment of celecoxib and colchicine resulted in prompt defervescence and dramatic reductions of pain. The patient was painless at an outpatient visit 6 month after the beginning of the treatment. [Case2] A 93-year-old man was admitted for acute severe low back pain, left hip pain, left knee pain and fever. Arthrocentesis of knee revealed CPPD crystals. MRI of the spine showed enhancement at the L2 and L3 vertebral bodies and the intervertebral disk. The patient responded to celecoxib and colchicine dramatically. [Conclusion] CPPD deposition disease can present as cervical and lumbar vertebral osteomyelitis.

#### W46-4

##### Four cases of dermatomyositis (DM) complicated with interstitial pneumonitis (IP) and pneumomediastinum (PnM)

Hiroaki Mori, Takahiro Mizuuchi, Yusuke Yamamoto, Mayu Tago, Eri

Kimura, Haeru Hayashi, Koichiro Tahara, Tetsuji Sawada  
Department of Rheumatology, Tokyo Medical University Hospital, Tokyo, Japan

Conflict of interest: None

The number of PM/DM patients has been increasing. We report here 4 DM patients complicated by PnM. Case 1; A 54 y/o woman with fever and rash presented with progressive muscle weakness and dysphagia, despite steroid therapy, and developed IP and PnM, which were improved by cyclosporine (CyA). Case 2; A 45 y/o man with fever, rash, myalgia, dysphagia and IP developed PnM, subcutaneous emphysema (SE) and hemophagocytic syndrome, which were controlled by steroid pulse and CyA. Case 3; A 58 y/o man with fever, rash, myalgia, and IP presented with PnM and SE, despite treatment with steroid and CyA, which was controlled by IVCY (IV pulse cyclophosphamide). Case 4; A 49 y/o man with fever, rash, arthralgia and myalgia presented with respiratory failure due to DM-IP, PnM and SE, which was controlled by IVCY. All the 4 cases presented with periungual erythema and IP, and developed PnM a few months later after starting medication, which required 2 months to be controlled. Case 3/4 presented with typical DM symptoms including dysphagia, while myositis was not pathologically demonstrated by muscle biopsy in case 1/2. The elevated serum ferritin level was useful as activity marker. Prognosis of DM-IP with PnM is reportedly poor, adequate immunosuppression is considered to be mandatory.

#### W46-5

##### Incidence of tuberculosis in the patients with biologics-treated rheumatoid arthritis

Koji Harada<sup>1</sup>, Juri Tsukahara<sup>1</sup>, Yuto Kasahara<sup>1</sup>, Koichi Sumida<sup>1</sup>, Yukinari Yamaguchi<sup>1</sup>, Yasuhiro Akai<sup>2</sup>

<sup>1</sup>Department of Nephrology and Rheumatology, Rakuwakai-Otowa Hospital, <sup>2</sup>Center for Rheumatic Diseases, Nara Medical University Hospital

Conflict of interest: None

[Background] Biologic therapies represent a major advancement in the management of rheumatoid arthritis (RA). However, treatment of biologics has been recognized as a risk factor for the development of tuberculosis. We evaluated the incidence of tuberculosis among the RA patients after commencement of biologic therapy. [Method] Forty RA patients who received the biologic therapy were enrolled. We examined the incidence of tuberculosis and clinical feature of these patients. Interferon-γ release assay (IGRA) was measured by Quantiferon TB Gold® or TSPOT® assay. [Results] IGRA was positive in 10.0%(n = 4), and all of them were prophylactically treated with isoniazid 300 mg/day. After the initiation of biologics, 2 patients developed tuberculosis. However, there was no patient with reactivation of tuberculosis. One patient had miliary tuberculosis and another developed pulmonary tuberculosis. Both of them developed tuberculosis within 12 months after initiation of biologics, and 6-months and 1-year incidence of tuberculosis were 2.6% and 7.2%, respectively. Two patients who developed tuberculosis received infliximab and tocilizumab, respectively. [Conclusion] Biologics-treated RA patients had higher risk for the development of tuberculosis within 12 months of beginning biologics.

#### W46-6

##### Glycometabolism and fatty liver in gout or hyperuricemia patients

Ikuko Tanaka<sup>1</sup>, Takashi Kato<sup>2</sup>, Kunikazu Ogawa<sup>3</sup>, Motokazu Kai<sup>3</sup>, Hisaji Oshima<sup>4</sup>, Shigenori Tamaki<sup>1</sup>

<sup>1</sup>Nagoya Rheumatology Clinic, Initiative for Rheumatology and Osteoporosis, Nagoya, Japan, <sup>2</sup>Department of Radiology, National Center for Geriatrics and Gerontology, Obu, Japan, <sup>3</sup>Mie Rheumatology Clinic, Initiative for Rheumatology and Osteoporosis, Suzuka, Japan, <sup>4</sup>Department of Connective Tissue Disease, Tokyo Medical Center, National Hospital Organization, Tokyo, Japan

Conflict of interest: None

[Objectives] Over 50% of gout or hyperuricemia patients have BMI score over 25. Gout and hyperuricemia are considered as a risk factor of steatohepatitis. Thus, we estimated the relationship of glycometabolism

and fatty liver in gout/hyperuricemia patients. [Methods] This study was carried out on 901 male patients with gout/hyperuricemia (age 45±11). 487 patients were diagnosed as fatty liver using abdominal ultrasound. [Results and discussion] The HbA1c and FBS level increased significantly by aging ( $p < 0.0001$ ). 62 % of the gout/hyperuricemia patients were diagnosed fatty liver by abdominal ultrasound. The rates for grade of fatty liver were 26% in G1 (mild), 23% in G2 (moderate), and 13% in G3 (severe). BMI was 23.1 in G0, where patients don't have fatty liver, 25.4 in G1, 27.2 in G2, and 29.8 in G3. The mean of serum ALT (IU/L) level was 23 in G0, 31 in G1, 38 in G2, and 57 in G3. The mean of HOMA-R was 0.87 in G0, 1.47 in G1, 1.68 in G2, and 2.12 in G3. These three scores increased significantly by the increased grade of fatty liver ( $p < 0.0001$ ). These results suggest that active intervention is necessary for the patients with severe fatty liver, because increase of serum ALT, insulin resistance, and overeating are risk factors for the progress of steatohepatitis.

#### W47-1

##### **A case of granulocyte-colony stimulating factor (G-CSF) producing lung cancer with symptoms like adult onset Still's disease (AOSD)**

Shotaro Kawano<sup>1</sup>, Atsushi Tanaka<sup>1</sup>, Yojiro Arinobu<sup>1</sup>, Aya Koto<sup>1</sup>, Hiroki Mitoma<sup>1</sup>, Mitsuteru Akahoshi<sup>1</sup>, Hiroaki Niuro<sup>2</sup>, Hiroshi Tsukamoto<sup>1</sup>, Koichi Akashi<sup>1</sup>

<sup>1</sup>Department of Clinical Immunology, Rheumatology, and Infectious Diseases, Kyushu University Hospital, <sup>2</sup>Department of Clinical Education Center, Kyushu University Hospital

Conflict of interest: None

The patient was a 58-year-old man who was admitted to our hospital because of persistent high fever, arthralgia, myalgia and eruption. The laboratory examination showed leukocytosis (32,560 / $\mu$ l) and a high level of CRP (27.3 mg/dl) without any evidence of infection. RF (222 IU/ml) levels were very high. Computed tomography scans showed tumorous shadow in the right upper lobe of lung and lymphadenopathies in the mediastinum. PET-CT showed abnormally high uptake of <sup>18</sup>F-FDG not only at the lung tumor but also diffusely throughout the bone marrow. Biopsy specimens by bronchoscopy revealed lung cancer (adenocarcinoma, stage IIIA). Moreover, high concentrations of G-CSF (230 pg/ml) and IL-6 (95.6 pg/ml) in the serum were revealed, and the specimen of the tumor was stained positively with anti-recombinant human G-CSF monoclonal antibodies. So, we diagnosed G-CSF producing lung cancer. Because performance status was very poor, he was administered PSL (50 mg/body) and radiation therapy. The WBC count, CRP, G-CSF and IL-6 all decreased and symptoms improved after radiation therapy. G-CSF producing cancer is rare, but is a cause of fever of unknown origin with symptoms like AOSD.

#### W47-2

##### **A case of Good's syndrome presenting refractory oral ulcers as first symptom**

Aya Koto<sup>1</sup>, Atsushi Tanaka<sup>1</sup>, Yojiro Arinobu<sup>1</sup>, Shotaro Kawano<sup>1</sup>, Hiroki Mitoma<sup>1</sup>, Mitsuteru Akahoshi<sup>1</sup>, Hiroaki Niuro<sup>2</sup>, Hiroshi Tsukamoto<sup>1</sup>, Koichi Akashi<sup>1</sup>

<sup>1</sup>Department of Clinical Immunology, Rheumatology, and Infectious Diseases, Kyushu University Hospital, <sup>2</sup>Department of Clinical Education Center, Kyushu University Hospital

Conflict of interest: None

A 52-year-old Japanese woman was admitted to our hospital with a 1-year history of refractory oral ulcers as first symptom. Behçet's disease, SLE, pemphigus, allergy to prosthetic metals, and drugs were denied. Serological tests revealed low level of immunoglobulin (IgG 466 mg/dl, IgA 71 mg/dl, IgM 32 mg/dl). With the presence of thymoma, diagnosis of Good's syndrome was made. Flow cytometry analysis of peripheral blood showed apparent reduction of memory B cells and down-regulated expression of BAFF-R on B cells, which may be a cause of low serum levels of immunoglobulin. The prognosis of Good's syndrome is reported to be poor due to increased susceptibility to infection. So, we started supplement of immunoglobulin and prophylactic antibiotic to her.

#### W47-3

##### **A patient with dyspnea turned out to be suffering from acquired hemophilia**

Koji Kikkawa<sup>1</sup>, Yutaka Motohashi<sup>1</sup>

<sup>1</sup>Hidaka Hospital, <sup>2</sup>Heisei Hidaka Clinic

Conflict of interest: None

[Case] A 65-year-old female with suffering from breathing was admitted to Hidaka Hospital in October 20XX. She has presented with a diagnosis of rheumatoid arthritis (RA) for over 40 years and had been treated with gold sodium thiomalate until 20XX-2 and with predonine (PSL) 10mg/day since then. She had reduced PSL since September 20XX and purpura appeared in her legs that she didn't care. Intramuscular hematoma was found on computed tomography eventually. Laboratory exams showed activated partial thromboplastin time (APTT) of 62 sec (reference range, 26 – 38 sec). APTT cross mixing test indicated acquired hemophilia. And factor VIII activity was under 1.0%(reference range, 78 – 165%) and factor VIII inhibitor was high. We treated her dyspnoea with PSL 15mg/day, but new purpura appeared. After diagnosis of acquired hemophilia, we dosed PSL 50mg/day. Then purpura disappeared and laboratory data improved. [Conclusion] Acquired hemophilia is not known among RA patients. Therefore physician should notice and treat immediately.

#### W47-4

##### **A case of polymyositis after injection of human papillomavirus vaccine**

Kensuke Irino, Kazutoshi Yukawa, Asako Oguma, Takuya Sawabe  
Department of Rheumatology, Hiroshima Red Cross Hospital and Atomic-Bomb Survivors Hospital, Hiroshima, Japan

Conflict of interest: None

A 19-year-old female patient was consulted to our hospital because of proximal muscle weakness, myalgia and the elevation of creatine phosphokinase (CK) after injection of human papillomavirus vaccine. She was admitted to our hospital to evaluate these symptoms. After the admission, an MRI showed high intensity area at right deltoid muscle. An electromyogram demonstrated myogenic pattern, and a muscle biopsy finding revealed an infiltration of leukocytes. She fulfilled the diagnostic criteria of polymyositis. There were no complications of malignancy. The symptoms were getting better gradually, therefore she was carefully followed without medication. Recently, there are several case reports of patients who suffered from pain, fatigue, and so many symptoms after vaccination of human papillomavirus. In our country, these patients are proposed to be classified as human papillomavirus vaccination associated with neuropathic syndrome (HANS). HANS is reported to be demonstrated with some symptoms like rheumatic diseases. It is probable that our present case was also associated with injection of the vaccine.

#### W47-5

##### **An autopsy case of multiple cerebral infarction and subarachnoid hemorrhage developed from rapidly progressive loss of visual acuity**

Kanako Watanabe, Toshio Odani, Shun Tanimura, Michihito Kono, Shinji Fukaya, Tsuyoshi Takeda, Hideaki Kikuchi  
Obihiro-Kosei General Hospital

Conflict of interest: None

A 65-year-old man, who had medical history of diabetes, complained of loss of left visual acuity. He was treated with steroid pulse therapy, but became blindness. Then his right eyesight also declined. Because this symptom repeated relapse with tapering steroid therapy, he was consulted to Neurology department. MRI revealed multiple infarctions in the left cerebral hemisphere and stenosis of the left internal carotid artery. Because cerebral infarction progressed despite antithrombotic therapy, he was consulted to our department. By diagnosing primary angitis of the central nervous system, he was treated with intravenous immunoglobulin therapy in combination with methotrexate administration. However, disturbed consciousness and quadriplegia progressed, and he died by subarachnoid hemorrhage. Pathological autopsy showed invasion of aspergillus in vascular walls of the left internal carotid and posterior cerebral

arteries, and we finally diagnosed as intracranial invasive aspergillosis from the sphenoid sinus. This is a rare disease, showing similar symptomatic course to that in vasculitis or idiopathic optic neuritis. It was supposed that symptoms of this case were likely caused by intracranial invasive aspergillosis on the background of immunocompromised host by diabetes.

#### W47-6

##### **A case report that GLP-1 receptor agonist makes good effect for not only diabetes mellitus but also rheumatoid arthritis**

Shun Ito<sup>1</sup>, Hisae Kawamitsu<sup>1</sup>, Yusuke Miyagawa<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Sagamihara Red Cross Hospital, <sup>2</sup>Department of Orthopedics, Sagamihara Red Cross Hospital

Conflict of interest: None

The case is 44 female. She was diagnosed with RA on 2007, and she was treated by SASP + PSL 3mg/day in other hospital. She had allergy for MTX and BUC. She was suggested to receive biochemical drug, but she rejected it for economic reason. The activity of RA keeps high activity, so GST was induced. When GST was started, DAS 28 score was 5.90, but after two years, DAS 28 was not improved. She have diabetes mellitus from 2010, and treated by basal bolus insulin therapy in other clinic, but her HbA1c level was around 10%. For control of DM, she was introduced our hospital on 2013. Her height was 158cm, weight was 69.9kg, and BMI was 28.0kg/m<sup>2</sup>. Her level of insulin secretion was still kept, so we changed from insulin to exenatide, GLP-1 receptor agonist. After exenatide therapy, HbA1c was improved from 9.7% to 7.5%(3 months), 5.8%(6 months), and CRP was improved from 0.35mg/dl to 0.21 mg/dl (3 months), 0.11mg/dl (6 months), and SDAI, marker of RA control, was also improved from 27.5 to 24.1 (6 months), 15 (1 year), though the treatment of RA was not change. GLP-1 receptor antagonist have a lot of effects. In this case, exenatide shows possibility of improvement about RA control.

#### W48-1

##### **Myositis-specific and myositis-associated autoantibody profiles and their clinical features with polymyositis and dermatomyositis**

Aki Nishioka<sup>1</sup>, Takeo Abe<sup>1</sup>, Yuichi Yokoyama<sup>1</sup>, Tetsuya Furukawa<sup>1</sup>, Takahiro Yoshikawa<sup>1</sup>, Takuya Hino<sup>1</sup>, Atsushi Saito<sup>1</sup>, Masahiro Sekiguchi<sup>1</sup>, Naoto Azuma<sup>1</sup>, Masayasu Kitano<sup>1</sup>, Shinichiro Tsunoda<sup>1</sup>, Kiyoshi Matsui<sup>1</sup>, Hajime Sano<sup>1</sup>, Yuji Hosono<sup>2</sup>, Koichiro Ohmura<sup>2</sup>, Tsuneyo Mimori<sup>2</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, <sup>2</sup>Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine

Conflict of interest: None

**[Objectives]** We examined the myositis-specific autoantibodies and myositis associated autoantibodies in patients with polymyositis and dermatomyositis. And we were examined for their clinical features **[Methods]** We investigated the myositis-specific autoantibodies and myositis-associated antibodies of 76 polymyositis and dermatomyositis patients. And we were analyzed retrospectively. **[Results]** Myositis-specific autoantibodies were positive in 30 cases. In addition, myositis associated autoantibodies was positive in 6 cases. Among them, the anti-ARS antibody was positive in 13 patients. Anti-MDA-5 antibody in 10 cases are positive, anti-TIF1- $\gamma$  antibody positive in 4 cases, anti-Mi-2 antibody in the two cases were positive. 11 patients with anti-ARS antibody-positive had merged the interstitial pneumonia as clinical symptoms. 90% of patients with anti-MDA-5 antibody positive is ADM, that all cases were admitted IP. All of the anti-TIF1- $\gamma$  antibody-positive cases admitted rash, those of 50% of the cases were complicated with malignant tumor. 3 patients died, all cases were anti-MDA-5 antibody-positive cases. **[Conclusion]** Through the measure myositis-specific autoantibodies, we have made it possible to predict the prognosis and complications of the disease early.

#### W48-2

##### **Analysis of Clinical Manifestations and Myositis-Specific Autoantibodies Associated with Severity of Physical Dysfunction after Treatment for Polymyositis and Dermatomyositis**

Hidenaga Kawasumi, Takahisa Gono, Yasushi Kawaguchi, Yasuhiro Katsumata, Sayuri Kataoka, Hisae Ichida, Akiko Tochimoto, Masanori Hanaoka, Yuko Okamoto, Hisashi Yamanaka  
Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: None

**Objectives** Half of all PM/DM patients have muscle weakness after initial treatment. We clarified the clinical manifestations and myositis-specific autoantibodies that are associated with the physical dysfunction after treatment in PM/DM. **Methods** Seventy seven patients with new-onset PM, DM or CADM were retrospectively enrolled. We obtained clinical data from their medical records. We evaluated the physical dysfunction after treatment using the J-HAQ on an outpatient basis. **Results** The median age of disease onset was 46 years old, and 79% were female. Anti-ARS, anti-MDA5, and anti-SRP were identified in 22, 7, and 9 patients, respectively. The median score of J-HAQ-DI was 0.125 (range 0-2.75). In a multivariate analysis, the age of disease onset ( $P=0.003$ ), gender ( $P=0.0075$ ), and the levels of CK prior to treatment ( $P=0.019$ ) were significantly associated with the J-HAQ-DI score after treatment. Anti-SRP positivity was significantly associated with high score of J-HAQ-DI. **Conclusion** The higher age of disease onset, female status, and the higher levels of CK prior to treatment were significantly associated with the severe physical dysfunction after treatment in PM/DM. Anti-SRP positive patients also have severe sustained physical dysfunction.

#### W48-3

##### **Clinical manifestations of clinically amyopathic dermatomyositis (CADM)**

Nobuhiro Sho, Mei Tani, Kako Kodama, Yu Matsueda, Eisuke Ogawa, Yoshiyuki Arinuma, Tatsuhiko Wada, Tatsuo Nagai, Sumiaki Tanaka, Shunsei Hirohata  
Kitasato University Infection and Collagen Disease

Conflict of interest: None

**[Objective]** CADM are often complicated with rapidly progressive interstitial lung disease (RP-ILD). Anti-CADM-140 antibody is strongly correlated with CADM. Our aim is to study the relationship between clinical manifestations of CADM and anti-CADM-140 antibody. **[Method]** Nine CADM cases that admitted to our hospital from 2011 to 2014 were analyzed retrospectively. We investigated clinical characteristics, including anti-CADM-140 antibody. **[Result]** All cases had Gottron's sign and 6 had heliotrope eyelids and mechanic's hands. Mean CK was 165 IU/l. All cases had ILD. Pulmonary consolidation adjacent to pleura was detected in 6. Mean PaO<sub>2</sub>/FiO<sub>2</sub> (P/F) on admission is 335. Anti-CADM-140 antibodies were detected in 7 of 8 (88%). We treated all with corticosteroid and cyclosporine, 7 with cyclophosphamide. Seven cases improved. Two cases died of RP-ILD. P/F on admission is less than 300 in both. Antibody could be followed up in 5. The titer decreased in 4, but didn't in 1 who died. Antibody was not detected in 1 who died. **[Conclusion]** We confirmed clinical diagnosis of CADM is strongly correlated with anti-CADM-140 antibody. For remission of CADM with ILD, we should promptly decide to initiate early aggressive therapy based on not only anti-CADM-140 antibody, but also clinical manifestations.

#### W48-4

##### **The analysis of the risk factors for the relapse in the patients with polymyositis (PM) or dermatomyositis (DM)**

Yosuke Asano<sup>1</sup>, Ken-ei Sada<sup>1</sup>, Yoshia Miyawaki<sup>1</sup>, Michiko Morishita<sup>1</sup>, Keiji Ohashi<sup>1</sup>, Haruki Watanabe<sup>1</sup>, Takayuki Katsuyama<sup>1</sup>, Eri Katsuyama<sup>1</sup>, Mariko Narazaki<sup>1</sup>, Noriko Toyota Tabebe<sup>1</sup>, Katsue Sunahori Watanabe<sup>1</sup>, Koichi Sugiyama<sup>1</sup>, Hiroshi Wakabayashi<sup>1</sup>, Tomoko Kawabata<sup>1</sup>, Jun Wada<sup>1</sup>, Hirofumi Makino<sup>2</sup>

<sup>1</sup>Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, <sup>2</sup>Okayama University Hospital, Okayama, Japan

Conflict of interest: None

[Objectives] To unravel risk factors of relapse in patients with polymyositis (PM) or dermatomyositis (DM). [Methods] Twenty one remitted patients (PM: 8, DM: 11, clinically amyopathic DM: 2) from 2010 to 2014 were recruited retrospectively. Demographics, clinical parameters, and treatment were compared between relapsed and non-relapsed patients. [Results] Mean age was 60 years (10 male and 11 female) and 3 patients complicated malignancy. Muscle biopsy was performed in 17 patients and 41% were diagnosed as myositis histologically. During a mean observation period of 430 days, 48% were relapsed. Female (70% vs 36%) and DM (70% vs 36%) were more frequent in relapsed group. The level of serum creatine kinase at onset was lower (1998 vs 4312 IU/L) and the level of ferritin at onset was higher (851 vs 282 ng/ml) in the relapsed group. The relapsed patients had histological diagnosis less frequently (25% vs 55%). The initial dose of glucocorticoids was lower while concomitant immunosuppressant use was more frequent in the relapsed patients (0.74 vs 0.83 mg/kg/day and 70% vs 36%, respectively). These comparison could not show any statistical differences. [Conclusion] The insufficient initiation therapy may contribute the relapse for the patients whose disease activity was underestimated.

#### W48-5

##### Characteristics of dermatomyositis or polymyositis with interstitial pneumonia

Noriko Hayami, Yoshifumi Ubara, Junichi Hoshino, Tatsuya Suwabe, Keiichi Sumida, Koki Mise, Toshiharu Ueno, Akinari Sekine, Rikako Hiramatsu, Eiko Hasegawa, Naoki Sawa, Kenmei Takaichi  
Rheumatology, Toranomon Hospital

Conflict of interest: None

[Objectives] We studied to investigate the characteristics of patients with dermatomyositis (DM) or polymyositis (PM) who had interstitial pneumonia (IP). [Method] Eleven patients with DM or PM who had interstitial pneumonia (IP) in our hospital from January 1994 to October 2014 were enrolled. We measured anti ARS antibody and anti CADM-140 antibody. Clinical characteristics and clinical course after treatment were evaluated. [Results] Patients with DM was 8, include patients with clinically amyopathic dermatomyositis (CADM) who have less muscle symptom, and patients with PM was 3. Autoantibodies were positive in seven patients of 11. Two patients with CADM were anti CAMD-140 antibody positive and had high level of serum ferritin. Recurrence was seen in four patients, and three patients who were anti ARS antibody positive improved by steroid therapy, and one patient who was auto antibody negative died of acute exacerbation of IP. [conclusions] Patients with CADM were anti CADM-140 antibody positive and had high level of serum ferritin, was predicted aggravation of rapidly progressive IP and poor prognosis. We treated them by corticosteroid and were able to obtain good course. Patients with anti ARS antibody-positive had much recurrence, but the treatment reactivity was good.

#### W48-6

##### Comparison of tests results between anti-Jo1 antibody, anti-ARS test and EUROLINE Myositis profile 3 to detect anti-synthetase antibodies in connective tissue disease patients

Koichiro Shinoda, Hirofumi Taki, Ryuji Hayashi, Shoko Matsui, Hiroyuki Honoki, Reina Tsuda, Maiko Obi, Satoshi Yamaguchi, Atsushi Matsui, Kazuyuki Tobe  
First Department of Internal Medicine, University of Toyama, Toyama, Toyama, Japan

Conflict of interest: None

[Objectives] Anti-synthetase antibodies (ASAs) are useful in the diagnosis of inflammatory myopathy (IM). To date, eight ASAs have been found. Anti-Jo-1 is the most, anti-PL-7, PL-12, EJ, OJ and KS occur in < 5% of IM patients. So far all antibodies had not been routinely detected except for anti-Jo-1, and we had used 'Myositis Profile 3'(EUROLINE), semiquantitative immunoblot which can detect eleven autoantibodies against Jo-1, PL-7, PL-12, EJ, OJ and others. Recently new assay to detect multiple ASAs (anti Jo-1, PL-7, PL-12, KS, EJ), called 'anti-ARS

test' had been developed in Japan. We compared the tests results between anti-Jo1 antibody (FEIA), anti-ARS test and Myositis Profile 3 to detect ASAs in connective tissue disease (CTD) patients. [Methods] All 3 tests were performed in CTD and interstitial pneumonitis (IP) patients. [Results] Each of 3 tests were positive in 39 patients, which include IIM (19 cases), IP (9), SJS (4) and others. Anti-Jo-1 were positive in 17 cases and other ASAs were in 18 cases. Although the results of Myositis Profile 3 was determined as +, ++, or +++, 4 cases of + results about anti-PL-7, PL-12, EJ was all negative in anti ARS test. [Conclusion] Tests results of ASAs was slightly different in different assays.

#### W49-1

##### Clinical study of dysphagia caused by inflammatory muscle disease

Shin-ichiro Omura, Rei Ito, Toshiaki Miyamoto  
Seirei Hamamatsu General Hospital

Conflict of interest: None

[methods] We analyzed eleven patients of inflammatory muscle disease who complained of dysphagia (D group) and compared with 74 patients who did not complained of dysphagia (IM group). [Results] In D group, 10 patients were female. The median age was 62.1 years old and older than IMD group (P<0.05). Median CPK was 3501 and median MMT was 3.18. Eight patients merged with malignancy. D group had lower MMT (P<0.05) and significant merger with malignancy (P<0.001). We have not seen statistically difference of the median interval between the initiation of other clinical manifestation and the onset of dysphagia between the groups, but four patients needed tubal feeding. Ten patients received prednisolone and two of them received immunosuppressive drugs. One patient did not received prednisolone and recovered because of Intravenous immunoglobulin and surgery. Two patients with malignancy were resistant of treatment, but improved after the surgery. After all, all patients can feed on foods. Only one patient occurred aspiration pneumonia during hospitalization. [Conclusion] Almost IMD patients who complained dysphagia merge with malignancy and had more muscle weakness than IMD who did not complained dysphagia. It is important to detect malignancy for IMD patients who complained of dysphagia.

#### W49-2

##### Clinical features of cardiomyositis associated with polymyositis or dermatomyositis

Hiroshi Ebe, Hiroto Tsuboi, Izumi Kurata, Hidenori Takahashi, Mizuki Yagishita, Saori Abe, Yuko Kurashima, Shunta Kaneko, Hoshimi Kawaguchi, Hiroyuki Takahashi, Masahiro Yokosawa, Hiromitsu Asashima, Shinya Hagiwara, Tomoya Hirota, Naoto Umeda, Yuya Kondo, Hiroshi Ogishima, Takeshi Suzuki, Isao Matsumoto, Takayuki Sumida  
Department of Internal Medicine, Faculty of Medicine, University of Tsukuba

Conflict of interest: None

[Objective] To clarify the clinical features of cardiomyositis (CM) associated with polymyositis (PM) or dermatomyositis (DM). [Methods] We examined 35 patients (Pts) with new onset PM/DM (20/15 Pts) who had been admitted to our department from Jun 2010 to Sep 2014, about 1) complication of CM, 2) clinical background, 3) laboratory findings, 4) clinical course, and 5) response to treatment, retrospectively. CM was defined as elevations of myocardial enzymes (ME) and abnormal findings in cardiac ultrasonography (CUS), or pathology of CM by biopsy. [Results] 1) CM was involved in 5 (PM/DM; 3/2) of 35 Pts (14%). 2) Malignancies (MG) were significantly more frequent in patients with CM than in without CM (2/5 vs 1/30, P=0.047), however, other features were similar between groups. 3) The serum CK, CK-MB, ME, pro-BNP, and autoantibodies were comparable between groups. 4) 2 Pts with MG developed CM earlier (1.5±0.7 months after myositis onset) than other 3 Pts without MG (12±7 months). 5) In all 5 Pts, elevations of ME and abnormal findings in CUS were improved by mPSL pulse (n=3), IVCY (n=1) or IVIG (n=2). [Conclusion] CM associated with PM/DM developed more frequently and earlier in Pts with MG than in without MG. Immunosuppressant and IVIG were effective for CM.

### W49-3

#### The clinical features of DM patients with malignancy

Hidenori Takahashi, Hiroshi Ogishima, Mizuki Yagishita, Izumi Kurata, Saori Abe, Yuko Kurashima, Shunta Kaneko, Hiroshi Ebe, Hiroyuki Takahashi, Hiromitsu Asashima, Masahiro Yokosawa, Shinya Hagiwara, Tomoya Hirota, Naoto Umeda, Yuya Kondo, Hiroto Tsuboi, Takeshi Suzuki, Isao Matsumoto, Takayuki Sumida  
Department of Internal Medicine, Faculty of Medicine, University of Tsukuba

Conflict of interest: None

[Objectives] To analyze the clinical features of DM patients with malignancy. [Methods] 1) We extracted 45 DM patients who were hospitalized at the University of Tsukuba Hospital from 2007 to 2014. 2) We divided them into responder and non-responder groups by the criteria of the PS score improvement after treatment. 3) We compared the gender, age of onset, baseline PS score and CK between responder and non-responder. [Results] 1) There were eight DM patients associated with malignancy. 2) The number of responder was 3 patients and non-responder was 5. 3) All responder patients were females but all non-responder patients were men ( $p = 0.02$ ). The mean ages of the responder and non-responder group were  $59.0 \pm 10.6$  and  $69.7 \pm 3.7$ , respectively (NS). Baseline PS scores in responder and non-responder group were  $2.3 \pm 0.9$  and  $3.6 \pm 0.5$ , respectively (NS). CK values in responder and non-responder were  $628 \pm 180$  U/l and  $2,623 \pm 1,617$  U/l, respectively. [Conclusion] In responder group of DM patients with malignancy, female was significantly increased compared with non-responder. Younger age, lower baseline PS score and milder CK titer was tendency to be associated with the good response to the treatment.

### W49-4

#### Clinical characteristics and treatment response of inflammatory myopathy (IM) associated with malignancy

Satomi Kobayashi<sup>1</sup>, Kazuyoshi Ishigaki<sup>2</sup>, Hou Chin<sup>1</sup>, Yasunobu Takizawa<sup>1</sup>, Keigo Setoguchi<sup>1</sup>

<sup>1</sup>Department of Allergy and Immunological Diseases, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan, <sup>2</sup>Department of Allergy and Rheumatology, The University of Tokyo Hospital, Tokyo, Japan

Conflict of interest: None

[Objectives] To clarify the characteristics of IM associated with malignancy and the change of IM manifestations after cancer treatment. [Methods] The records of the patients with IM except for inclusion body myopathy who had been admitted to our hospital in the past 14 years were reviewed. [Results] Seventy patients with IM were identified. Twenty-two of 70 (31.4%) patients had malignancy, including gastric, lung, breast, ovarian cancer, adult T-cell leukemia (ATL) and so on. Eighteen of 22 patients with malignancy took not only cancer treatment but also steroid therapy for IM. In three of 18 patients, their manifestations were improved after chemotherapy. Four of 22 patients with malignancy took only cancer treatment. Three received chemotherapy including steroid. In two of three, the manifestations were improved. One ATL patient treated with chemotherapy without steroid reached complete remission of ATL and the CK level was improved. There were no patients whose manifestations were improved only by operation. Eighteen patients with malignancy were followed up, and 12 (66.6%) patients died. Eight (44.4%) patients died of malignancy. [Conclusion] The manifestation of IM is improved by cancer treatment in some IM patients with malignancy. Many of them had received chemotherapy.

### W49-5

#### Clinical and liver biopsy findings in 13 cases of idiopathic inflammatory myopathies

Kazuhiro Furuya, Masayuki Yoshiga, Kentaro Noda, Taro Ukichi, Ken Yoshida, Isamu Kingetsu, Daitaro Kurosaka  
Division of Rheumatology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Background] In the idiopathic inflammatory myositis (IIM), aspartate aminotransferase (AST) is usually elevated in the serum as a myogenic enzyme, not as a hepatogenic enzyme. But in some cases of IIM, other common hepatogenic enzymes may be elevated in the serum. [Objectives and Methods] We retrospectively extracted all 13 cases admitted to our hospital due to IIM and underwent liver biopsy during the period of 2007 to 2014, and evaluated the histopathological and clinical aspects. [Results] The case group comprised 3 men and 10 women and the mean age was 55.5 years, and comprised 8 cases of polymyositis and 5 dermatomyositis. The mean serum creatine kinase (CPK) level was 2251 IU/l, and the mean serum AST, ALT, ALP, and  $\gamma$ -GTP levels were 184.2 IU/l, 142.3 IU/l, 314.8 IU/l, and 71.9 IU/l, respectively. The histopathological findings in liver showed that autoimmune hepatitis (AIH) like changes was showed in 2 cases and primary biliary cirrhosis (PBC) like changes in 2 cases, and the 4 cases were every polymyositis patients. Other 6 cases only showed non specific mild liver damage, but none of all 13 cases show normal liver histology. [Conclusion] This study suggested that the cases of IIM, especially polymyositis, with liver damage may be likely to have AIH and/or PBC.

### W49-6

#### The availability of Nailfold Videocapillaroscopy (NVC) in patients with dermatomyositis and polymyositis (DM/PM)

Yasuyuki Todoroki<sup>1</sup>, Satoshi Kubo<sup>1</sup>, Kazuhisa Nakano<sup>1</sup>, Shingo Nakayama<sup>1</sup>, Shintaro Hirata<sup>1</sup>, Shunsuke Fukuyo<sup>1</sup>, Ippei Miyagawa<sup>1</sup>, Yurie Sato<sup>1</sup>, Shin Tanaka<sup>3</sup>, Minoru Satoh<sup>1,2</sup>, Kazuyoshi Saito<sup>1</sup>, Yoshiya Tanaka<sup>1</sup>

<sup>1</sup>The 1st Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, <sup>2</sup>Department of Clinical Nursing, School of Health Sciences, University of Occupational and Environmental Health, Kitakyushu, Japan, <sup>3</sup>Department of Human Information and Life Sciences, School of Health Sciences, University of Occupational and Environmental Health, Kitakyushu, Japan

Conflict of interest: None

[Objectives] NVC has been recently applied for the diagnosis of systemic sclerosis. However, the availability of NVC findings in patients with DM/PM is not established. The aim of this study is to investigate the association between NVC findings and clinical features. [Methods] 17 patients with DM/PM (13 DM/ 4 PM) were enrolled. NVC findings, clinical features and serum autoantibody profiles were assessed. [Results] 9 showed changes in NVC observation. There were no differences between DM and PM. Similarly, no significant differences were observed between the patients with or without Raynaud's phenomenon, heliotrope rash, Gottron's papules, arthritis, and the severity of interstitial pneumonia (CT score). However, in 8 amyopathic dermatomyositis (CADM) patients, 6 (75%) showed NVC changes. Only 20% of the patients with anti-ARS antibody, which is good prognosis factor, showed NVC changes, whereas 67% of the patients with anti-MDA-5 antibody showed NVC changes ( $p=0.07$ ). [Conclusion] About half of DM/PM showed NVC changes. The incidence of NVC changes was higher in CADM and patients with anti-MDA-5, whereas that was lower in patients with anti-ARS. NVC appears to provide useful information in patients with DM/PM, contributing to identifying patients with a poor prognosis.

### W50-1

#### The Early initiation of Immunosuppressant is Beneficial for Long-Term Prognosis in Patients of Interstitial lung Disease with Anti-Synthetase Antibodies

Yuji Hosono, Koji Kitagori, Yoshitaka Imura, Ran Nakashima, Naoichiro Yukawa, Hajime Yoshifuji, Koichiro Ohmura, Takao Fujii, Tsuneyo Mimori

Department of Rheumatology and Clinical Immunology, Kyoto University

Conflict of interest: None

[Objectives] Immunosuppressants (IS) had been reported to improve outcome in anti-ARS-associated ILD. However, the efficiencies and long-term prognosis depending on the time of administration are still unclear. Here, we intended to investigate the benefits of early use of IS in

anti-ARS-positive ILD. [Methods] Clinical data and serum samples were collected from adult Japanese patients. Patients who were treated by IS (cyclosporine, tacrolimus and azathioprine) within 1 year from the initial treatment were defined as early-use group. Anti-ARS were screened using the RNA immunoprecipitation assay. Kaplan-Meier survival analysis was applied to compare overall mortality rates. [Results] 131 patients were anti-ARS-positive. 41 were early-use, 42 were delayed-use and 48 were no-IS-use group. The 15-year survival rate of early use group was the highest ( $P<0.05$ ). The rate of patients who needed home oxygen therapy was higher in delayed-use group than other groups (36%(15/42) vs 20%(8/41), 17%(8/48),  $P<0.05$ ). All cause of death except 1 was ILD exacerbation in delayed-use group, while there was none in early-use group and half in no-IS-use group. [Conclusion] The early use of IS in addition to high dose glucocorticoids should be strongly recommended for ILD patients with anti-ARS antibodies.

## W50-2

### Necessary intervention for asymptomatic myositis and necessary steroid dose for treating relapsed myositis

Yusuke Sugimori, Hiroyuki Yamashita, Hiroaki Hatano, Toshiaki Shimizu, Masanori Kono, Yuko Takahashi, Toshikazu Kano, Hiroshi Kaneko, Akio Mimori  
Division of Rheumatic Diseases, National Center for Global Health and Medicine, Tokyo, Japan

Conflict of interest: None

**Objectives:** To study necessary intervention for asymptomatic myopathy of polymyositis (PM) or dermatomyositis (DM), and necessary steroid dose for treating relapsed myositis. **Methods:** Hospital records in 1991-2014 were reviewed for 92 myositis patients. **Results:** I) A long-time asymptomatic period before initial therapy was found in 3 PM patients. A 71-year-old woman showed 500-800 IU/ml of serum CK levels and non-progressing myositis. Mild muscle weakness and dysphagia manifested at 76-yo, and the biopsy-proven myositis was successfully treated by high-dose steroid. A 59-yo woman having scleroderma showed asymptomatic myositis with 1500-7000 IU/ml of serum CK. Mild muscle weakness manifested at 61-yo with positive muscle MRI and EMG findings. High-dose steroid and gamma-globulin therapy led to remission. A 73-yo woman diagnosed with PM had shown asymptomatic serum CK elevation over 7 years before referral. II) Of our 92 patients with PM or DM, 43 patients developed relapsed myositis a mean 3.9 years after the remission. Prednisolone dose was 53 mg/day at a mean for initial therapy and 10-30 mg/day for relapsed myositis. **Conclusion:** Myositis should be treated even during the asymptomatic phase, and necessary steroid dose may be lower for relapsed myositis than initial dose.

## W50-3

### Clinical assessment of primary Tacrolimus therapy in patients with polymyositis or dermatomyositis complicated with interstitial lung disease

Masataka Nakamura, Tomoya Miyamura, Makiko Higuchi, Shoko Kodama, Soichiro Takahama, Yu Kaku, Rumi Minami, Masahiro Yamamoto, Eiichi Suematsu  
Department of Internal Medicine and Rheumatology, National Hospital Organization Kyushu Medical Center

Conflict of interest: None

[Objective] Interstitial lung disease (ILD) is an important complication to determine prognosis for patients with polymyositis or dermatomyositis (PM/DM). A previous study reported that primary intensive approach using immunosuppressive agents might improve their survival. Therefore, we here assessed the efficacy of the strategy initially using TAC to ILD-PM/DM. [Methods] We retrospectively examined medical records of eight ILD-PM/DM patients treated with early combination therapy of PSL and TAC from October 2013 to October 2014. [Result] Two patients were diagnosed as ILD-PM and the others were ILD-DM, including two clinically amyopathic DM. The positivity for anti-Jo-1 antibody and anti-ARS antibodies were 37.5% and 83.3%, respectively. HRCT in lung revealed that the characteristics of ILD were mostly GGO and consolidation but not honeycombing. Serum CK and KL-6 levels

were moderately increased at diagnosis. Primary combination therapy of PSL and TAC resulted in improvement of serum CK level and HRCT findings without recurrence despite tapering PSL. [Conclusion] Our results suggested that initial TAC exposure contributed to reduction in the amount of PSL and relapse prevention.

## W50-4

### Corticosteroid-sparing effect of tacrolimus in the initial treatment of dermatomyositis and polymyositis

Yusuke Yokoyama<sup>1</sup>, Shunsuke Furuta<sup>2</sup>, Kei Ikeda<sup>1</sup>, Koichi Hirose<sup>1</sup>, Hiroshi Nakajima<sup>1</sup>

<sup>1</sup>Allergy and Clinical Immunology, Chiba University Hospital, Chiba, Japan, <sup>2</sup>Clinical Research Center, Chiba University Hospital, Chiba, Japan

Conflict of interest: None

[Objectives] Catabolic effects of corticosteroids such as myopathy can be detrimental in polymyositis (PM) and dermatomyositis (DM) patients. We aimed to assess the corticosteroid-sparing effect of tacrolimus in the initial treatment for PM/DM. [Methods] We retrospectively identified 19 PM/DM patients who received initial treatment with 1mg/kg/day prednisolone (Conventional Monotherapy) and 23 patients with tacrolimus plus 0.8mg/kg/day prednisolone (Tacrolimus Combination). Data until 36 months after commencing treatment were collected. [Results] There were no statistically significant differences in baseline characteristics between two groups. Median daily dose of prednisolone in the Tacrolimus Combination group was significantly lower than that in the Conventional Monotherapy group at all time during the study period. The time required for creatine kinase normalization and relapse rate were comparable between two groups. The period of hospitalization for initial treatment was significantly shorter and survival without serious infection or relapse tended to be longer in the Tacrolimus Combination than the Conventional Monotherapy. [Conclusion] Tacrolimus has a corticosteroid-sparing effect and reduces the length of hospitalization period for the initial treatment of PM/DM

## W50-5

### A new therapeutic approach targeting IL-23 for inflammatory myositis

Natsuka Umezawa, Yoko Yoshihashi, Naoki Kimura, Akito Takamura, Kimito Kawahata, Hitoshi Kohsaka  
Department of Rheumatology, Tokyo Medical and Dental University, Tokyo, Japan

Conflict of interest: None

[Objectives] To investigate the pathogenesis and establish a novel therapy for idiopathic inflammatory myositis (IIM), we established previously C-protein induced myositis (CIM), an animal model of PM. In some experimental models of autoimmune diseases, IL-23-Th17 pathway plays an important role in the pathogenesis. Despite IL-17A had been shown as an effector molecule of IL-23-Th17 pathway in those models, IL-17A-null mice were susceptible to CIM in our previous experiment. Because IL-23 acts not only on the maintenance of Th17 cells, but also on the activation of the innate immunity, we hypothesized that IL-23 would act in CIM through mechanisms other than IL-17A. The purpose of this study is to investigate the role of IL-23. [Methods] We evaluated histological severity of CIM in IL-23-null mice. We examined the preventive and therapeutic effects of anti-IL-23R antibody in CIM. [Results] CIM in IL-23-null mice was significantly suppressed compared to WT. Both preventive and therapeutic administration of anti-IL-23R antibody ameliorated CIM. [Conclusion] Our results suggest that IL-23 should exert a pathogenic role in CIM independently of IL-17A and thus could be a possible therapeutic target for IIM.

## W50-6

### Long-term efficacy of autologous hematopoietic stem cell transplantation for refractory dermatomyositis

Hiroshi Tsukamoto<sup>1</sup>, Masahiro Ayano<sup>1</sup>, Hiroaki Niino<sup>2</sup>, Yojiro Arinobu<sup>1</sup>, Mitsuteru Akahoshi<sup>1</sup>, Hiroki Mitoma<sup>1</sup>, Atsushi Tanaka<sup>1</sup>, Shun-ichiro Ota<sup>1</sup>, Naoko Ueki<sup>1</sup>, Satomi Hisamoto<sup>1</sup>, Yuri Hirosaki<sup>1</sup>, Daisuke Oryoji<sup>1</sup>, Koichi

Akashi<sup>1</sup>

<sup>1</sup>Department of Clinical Immunology, Rheumatology, and Infectious Diseases, Kyushu University Hospital, Fukuoka, Japan, <sup>2</sup>Clinical Education Center, Kyushu University Hospital, Fukuoka, Japan

Conflict of interest: None

[Objectives] Acute/Subacute interstitial pneumonia (A/SIP) is often complicated with clinically amyopathic dermatomyositis (CADM) that shows the typical skin manifestations of DM but has no or little evidence of clinical myositis. A/SIP complicated with CADM is life-threatening and shows a rapidly progressive pattern with a 6-month survival rate of less than 50%, irrespective of intensive therapy. Patients with DM also complicate with refractory skin ulcer. The aim of the study is to investigate the long-term efficacy of autologous hematopoietic stem cell transplantation (auto-HSCT) for patients with refractory DM. [Methods] Three patients with refractory DM received auto-HSCT. A patient with DM only received peripheral blood stem cell harvest. [Results] Two patients (case 1 and 2) with SIP complicated with CADM dramatically improved after auto-HSCT. However, case 3 died due to progression of SIP before auto-HSCT. A huge skin ulcer complicated with case 4, cured six months after auto-HSCT. Case 1 and 3 had sepsis, and case 1 and 4 had CMV antigenemia. Case 1 and 4 have maintained remission for more than 8 years. In case 3, exacerbation of IP 30 months after HSCT was successfully treated with tacrolimus. [Conclusion] Auto-HSCT showed long-term efficacy in the treatment of DM.

### W51-1

#### Anti-Carbamylated Protein antibodies in Rheumatoid Arthritis patients of Asian descent

Kazuko Shiozawa<sup>1</sup>, Shunichi Shiozawa<sup>2</sup>

<sup>1</sup>Rheumatic Diseases Center, Kohnan Kakogawa Hospital, Kakogawa, Japan, <sup>2</sup>Department of Medicine, Rheumatic Diseases Unit, Kyushu University Beppu Hospital, Beppu, Japan

Conflict of interest: None

[Objectives] Anti-Carbamylated protein antibody (anti-CarP), recently found in RA, is found prior to disease onset, associates with the conversion towards arthralgia and with a more severe disease course in patients negative for anti-citrullinated protein (anti-CCP). Since anti-CarP has been described only in Caucasian, we studied anti-CarP in the Japanese RA patients. [Methods] Sera of 268 Japanese RA patients first visit to the Konan Kakogawa Hospital April 2003-March 2006 were measured for anti-CarP and compared with 324 healthy local controls. [Results] Anti-CarP was increased in RA as compared to control ( $449 \pm 544$  vs  $71 \pm 133$ , Mann-Whitney U test:  $P < 0.001$ ). Using the cut-off level 97% as in EAC study, anti-CarP had a sensitivity of 45.2% in RA. The patients were subdivided based on anti-CarP and anti-CCP2: 42.2% anti-CarP<sup>+</sup>CCP2<sup>+</sup>, 31.7% anti-CarP<sup>+</sup>CCP2<sup>-</sup>, 23.1% anti-CarP<sup>-</sup>CCP2<sup>-</sup> and 3.0% anti-CarP<sup>-</sup>CCP2<sup>+</sup> patients (11.4% of all CCP2<sup>-</sup> patients). Positivities are EAC 53%, EIRA 63%, and Japan 74%. [Conclusion] Anti-CarP is also present in Japanese RA patients. Importantly, also in Japanese cohort, the patients positive only for either anti-CarP or anti-CCP2 are present.

### W51-2

#### Anti-carbamylated protein antibodies are specific to rheumatoid arthritis, but less specific than ACPA

Toshiyuki Ota<sup>1,2</sup>, Ayumi Uchino<sup>2</sup>, Yusuke Kashiwado<sup>2</sup>, Shuji Nagano<sup>2</sup>

<sup>1</sup>Center for Rheumatology, Iizuka Hospital, Fukuoka, Japan, <sup>2</sup>Department of Internal Medicine and Rheumatology, Fukuoka, Japan

Conflict of interest: None

[Objectives] Carbamylation is one of the non-enzymatic reactions and results from the covalent binding of isocyanic acid to proteins. Antibodies to carbamylated proteins (ACarP) in rheumatic diseases, especially rheumatoid arthritis (RA) have lately attracted considerable attention. In this study we have analyzed the presence of ACarP in Japanese patients with RA or other rheumatic diseases and healthy controls, and further investigated the association with ACPA. [Methods] Carbamylated fibrinogen (FBG) was generated by incubating human FBG with potassi-

um cyanate. Citrullinated FBG was generated by reaction with human FBG in the presence of rabbit muscle PAD2 (Sigma) and CaCl<sub>2</sub>. ELISA was used to measure IgG antibodies. [Results] ACarP concentration revealed statistically higher in patients with RA than in patients with non-RA and healthy donors. Positive correlation of concentration between ACarP and ACPA was statistically significant, though somewhat discrepancy between them existed. We obtained the cut-off values using ROC analysis and found the sensitivity/specificity of ACarP and ACPA, 57.8/62.5% and 67.2/85.4%, respectively. Moreover area under the curve was 0.616 in ACarP and 0.737 in ACPA. [Conclusion] Measurement of ACarP might be useful for recognizing RA as a syndrome.

### W51-3

#### Are autoantibodies to DNA mismatch repair enzymes specific to inflammatory myopathy?

Yoshinao Muro<sup>1</sup>, Kazumitsu Sugiura<sup>1</sup>, Ran Nakashima<sup>2</sup>, Yuji Hosono<sup>2</sup>, Tsuneyo Mimori<sup>2</sup>

<sup>1</sup>Nagoya University Graduate School of Medicine, Nagoya, Japan, <sup>2</sup>Kyoto University Graduate School of Medicine, Kyoto, Japan

Conflict of interest: None

[Objectives] DNA mismatch repair (MMR) is one of several DNA repair pathways. Human MMR enzymes (MMREs) consist of MSH2, MSH3, MSH6, PMS1, PMS2, MLH1, and HLLH3. In 2001, autoantibodies to PMS1, PMS2 and MLH1 were reported as myositis-specific autoantibodies (MSAs). In 2005, anti-PMS1 and anti-MSH2 antibodies (Abs) were found also in Japanese patients (Pts) with dermatomyositis (DM)/polymyositis (PM). The present study evaluates the clinical implications of anti-MMREs in Pts with systemic autoimmune diseases. [Methods] Serum samples were collected from 160 Pts with DM, 57 with PM and 22 with myositis overlap syndrome (OS). 40 Pts with SLE, 20 with systemic sclerosis (SSc), 20 with RA and 20 with Sjögren's syndrome were also assessed. Recombinant 7 MMREs were applied to ELISA and immunoprecipitation (IPP). The autoAbs were confirmed by IPP-western. [Results] Anti-MMRE Abs were found in 9 Pts with DM, 3 with PM, 3 with OS and 3 with SLE. Antibodies to MLH1, PMS1, MSH2 and PMS2 were found in 12, 11, 4 and 2 Pts, respectively. Although 13 Pts had other disease-marker autoAbs, 5 Pts with monospecific anti-MMRE were restricted to idiopathic inflammatory myositis (IIM). [Conclusion] Although anti-MMRE Abs are not categorized into MSAs, their identification is important in IIM clinics.

### W51-4

#### Association of anti-CADM-140/MDA5 autoantibody and malignancy in Japanese patients with dermatomyositis

Shinji Sato, Takayoshi Kurabayashi, Sho Sasaki, Yasushi Koyama, Shinichi Nogi, Noriko Sasaki, Naofumi Chinen, Kiri Honda, Takayuki Wakabayashi, Chiho Yamada, Yasuo Suzuki

Tokai University, School of Medicine, Kanagawa, Japan

Conflict of interest: None

[Objectives] To examine the relationship between anti-CADM-140/MDA5 antibody and malignancy in patients with dermatomyositis (DM). [Methods] Fifty-two patients with classical DM (CDM) or clinically amyopathic dermatomyositis (CADM) were retrospectively evaluated for the associations between anti-CADM-140/MDA5 antibody and the occurrence of malignancy. [Results] Of 52 patients, 39 patients were diagnosed as having classical DM (male/female: 13/26) and 13 were diagnosed as having CADM (male/female: 1/12). Sera from 2 classical DM patients and all 12 patients with CADM were found to contain anti-CADM-140/MDA5 antibody (5% 2/39 vs. 92% 12/13,  $P < 0.0001$ ). Malignancy was found in only one patient with anti-CADM-140/MDA5 antibody positive, whereas 10 patients with anti-CADM-140/MDA5 antibody negative (7% 1/14 vs. 26%, 10/38,  $P = 0.25$ ). [Conclusion] Anti-CADM-140/MDA5 antibody was significantly found with a high frequency in patients with CADM compared with those with CDM. On the other hand, malignancy was less found in patients with anti-CADM-140/MDA5 antibody positive compared with those with anti-CADM-140/MDA5 antibody negative.



## W51-5

**Diagnostic value of anti-ARS antibodies in juvenile dermatomyositis**  
Shunichiro Takezaki, Yusuke Tozawa, Masahiro Ueki, Ichiro Kobayashi  
Department of Pediatrics, Hokkaido University Graduate School of Medicine

Conflict of interest: None

[Objectives] Anti-aminoacyl-tRNA synthetases (ARS) antibodies (Abs) comprises 20 Abs including anti-jo-1 Abs. The MESACUP anti-ARS test® (BML, Nagoya, Japan) which can detect 5 common anti-ARS Abs (anti-Jo-1, PL-7, PL-12, EJ and KS Abs) is currently available in Japan. Using the kit, anti-ARS Abs are detected in 29.5% of total adult DM patients and 18% of the patients without anti-jo-1 Abs, suggesting diagnostic values of the test in adult DM. The aim of this study is to evaluate the diagnostic value of the MESACUP anti-ARS test® in JDM. [Methods] 22 JDM patients, 22 other connective tissue disease (CTD) patients (11 SLE, 6 SLE with SS, 2 SSc, 2 MCTD and 1 MCTD with SS), who visited Hokkaido University Hospital, and 15 healthy controls were enrolled. Anti-ARS Abs were measured by the MESACUP anti-ARS test®. [Results] Anti-ARS Abs were not detected in any of 22 JDM patients, including 1 with low titers of anti Jo-1 Abs, 22 other CTD patients and 15 healthy controls by MESACUP anti-ARS test®. [Conclusion] Although the sample size was small, anti-ARS Abs are not prevalent in JDM and have a limited diagnostic value. Further studies involving larger number of JDM patients are necessary to clarify the sensitivity and clinical significance of the Abs in JDM.

## W51-6

**Novel autoantigens associated with lupus nephritis**  
Sachiko Onishi<sup>1</sup>, Jun Ishizaki<sup>1</sup>, Tatsuhiko Miyazaki<sup>2</sup>, Hitoshi Yamasaki<sup>1</sup>, Koichiro Suemori<sup>1</sup>, Takuya Matsumoto<sup>1</sup>, Masaki Yasukawa<sup>1</sup>, Hitoshi Hasegawa<sup>1</sup>  
<sup>1</sup>Department of Hematology, Clinical Immunology and Infectious Diseases, Ehime University Graduate School of Medicine, Ehime, Japan, <sup>2</sup>Department of Pathology, Gifu University Hospital, Gifu, Japan

Conflict of interest: None

[Objectives] To identify new autoantigens associated with the disease etiology and/or prognosis of lupus nephritis (LN). [Methods] Immunoprecipitation was performed using serum from patients with LN. Immunohistochemical staining of renal tissues was carried out with antibodies against proteins identified the immunoprecipitation. The specificity of the identified autoantigens was analyzed by ELISA with serum from various autoimmune diseases patients. C57BL/6 mice were injected intravenously with purified proteins and then their renal tissues were examined. [Results] Two LN-associated autoantigens, ribosomal RNA-processing protein 8 (RRP8) and spermatid nuclear transition protein 1 (TNP1), were identified by immunoprecipitation and immunofluorescence of renal tissue. Immune complex-deposited glomerulonephritis was also recognized in C57BL/6 mice injected with RRP8 or TNP1. Among SLE patients, 63.6% and 45.5% of those with LN were positive for anti-RRP8 and anti-TNP1 antibodies respectively, compared with 12.5% and 9.4% of SLE patients without nephritis. [Conclusion] We have identified RRP8 and TNP1 as new LN autoantigens. RRP8 and TNP1 may play an important role in the pathogenesis of LN. These autoantibodies may be useful for prediction and monitoring of LN.

## W52-1

**Questionnaire survey a long-term after forefoot surgery in the patients with rheumatoid arthritis**  
Tomo Oyakawa, Hajime Ishikawa, Satoru Kodama, Kengo Harigane, Daisuke Kobayashi, Asami Abe, Hiroshi Otani, Satoshi Ito, Kiyoshi Nakazono, Akira Murasawa  
Department of Rheumatology, Niigata Rheumatic Center, Niigata, Japan

Conflict of interest: None

[Objectives] To investigate a long-lasting effect of forefoot surgery in the patients with rheumatoid arthritis (RA), a questionnaire survey was performed. [Methods] A questionnaire was sent to 39 patients who under-

went forefoot surgery between June 2001 and November 2006. As for the operative method, 96% was the 1st MTP joint Swanson implant arthroplasty, the 2nd to the 5th shortening oblique osteotomy of metatarsal neck. Present condition of the surgically-treated foot, satisfaction level, and reasons of satisfying or unsatisfying were inquired. [Results] The answers were provided from 58 feet in 34 patients (87.1%). The mean age at survey was 57.1 years old. About the usefulness, 94.8% of the patients answered "better" than the preoperative condition. In satisfaction level, 94.8% answered "most satisfying" or "satisfying". Disease Activity decreased in comparison with that at the time of surgery. The most frequent reason of satisfying was "pain relief". The reason of unsatisfying was "deteriorated appearance" and "difficulty in walking" and "recurrent callosity". [Conclusion] A long-lasting favorable effect of the forefoot surgery was expected on the patients with severe forefoot deformity.

## W52-2

**Hallux alignment after metatarsal shortening osteotomy without hallux for rheumatoid lesser toe deformity**  
Akihide Nampei, Yoshio Nagayama  
Department of Orthopaedic Surgery and Rheumatology, Osaka Rosai Hospital

Conflict of interest: None

[Background] Among the rheumatoid forefoot deformity, occasionally, the hallux MTP joint may have minimal deformity. Resection arthroplasty of lesser MTP joint without hallux surgery is unfavorable because of the high probability of deterioration of hallux valgus deformity. We examined the hallux alignment after shortening metatarsal osteotomy of lesser toe. [Methods] Seven feet were included. All patients were RA and female, with a mean age of 70 years. Metatarsal shortening osteotomy from 2nd to 5th toe without great toe were underwent. JSSF scale, hallux valgus angle (HVA), intermetatarsal angle (IMA), sesamoid position (Hardy grade), shortened length of 2nd metatarsus were examined. Mean follow-up period were 18 months. [Results] Mean JSSF lesser toe scale was improved from 16 to 76. HVA and IMA were deteriorated from 17.0 to 22.9, and from 6.7 to 9.7 respectively. Three cases, who have over 18 degree HVA, over Hardy grade 3, over 8 mm 2nd metatarsus shortend, showed over 25 degree HVA at final follow-up. [Conclusion] Although patients with RA lesser toe deformity with minimal hallux MTP deformity, shortening and corrective surgery of great toe is needed for the patients who have over 18 degree HVA, over grade 3 Hardy classification, and over 8 mm shortening of 2nd metatarsus.

## W52-3

**Changes in plantar pressure after toe plasty in the patients with rheumatoid arthritis**  
Kengo Harigane<sup>1,2</sup>, Hajime Ishikawa<sup>1</sup>, Hiroshi Otani<sup>1</sup>, Asami Abe<sup>1</sup>, Tomo Oyakawa<sup>1</sup>, Satoshi Ito<sup>1</sup>, Daisuke Kobayashi<sup>1</sup>, Satoru Kodama<sup>1</sup>, Kiyoshi Nakazono<sup>1</sup>, Akira Murasawa<sup>1</sup>, Tomoyuki Saito<sup>2</sup>  
<sup>1</sup>Department of Rheumatology, Niigata Rheumatic Center, <sup>2</sup>Department of Orthopaedic Surgery, Yokohama City University

Conflict of interest: None

[Objectives] The objective of this study is to investigate the serial change in plantar pressure during one year after toe plasty and to clarify the effectiveness of toe plasty for the treatment of painful callosities. [Methods] Thirty RA 30 feet in 23 patients with rheumatoid arthritis were included into this prospective study. Toe plasty was performed between our hospital from April 2012 and April 2013. Peak pressure and time integrated pressure were measured using F-scan II® 2 before surgery, 1, 3, 6, and 12 months after surgery. In addition, they were compared with those in 36 healthy controls. [Results] Both pressures peak pressure shifted from rearfoot segment to forefoot segment was observed gradually between 3 and 12 months after surgery. This may be because Bbone union at the site of osteotomy was obtained and painful callosities disappeared at about 3 to 6 months after surgery. [Conclusion] At 12 months after surgery, time integrated pressure in midfoot segment at 12 months after surgery in the patients with RA was significantly higher than those in healthy controls, because of which may be explained by residual flat-foot deformity in the patients with RA.

## W52-4

### Short term outcome of metatarsal head preserving distal shortening oblique osteotomy for forefoot deformities in patients with rheumatoid arthritis

Yuichi Nagase, Hiroshi Takahashi, Yoshio Uchida, Takuji Nishikawa  
Tokyo Metropolitan Bokutoh Hospital

Conflict of interest: None

[Objectives] We will report short term result of metatarsal head preserving distal shortening oblique osteotomy for forefoot deformities in patients with rheumatoid arthritis (RA). [Methods] of 27 patients, 36 feet with RA were treated by this procedure from January 2012 to May 2014. The mean age was 65 years old (46-78 years), and the mean follow up period was 21.6 months (3-31 months). We investigated AOFAS score for clinical outcome and radiographic assessment for the deformities and bone union. [Results] AOFAS score for great toe was significantly improved from 43.9 to 78.7 and that score for lesser toe was significantly improved from 30.7 to 77.8. Hallux valgus angle was improved from 47.5 degree to 18.1 degree. Bone union of great toe was 100% (30/30 toes) and that of lesser toe was 93.7% (165/176 toe). There were no clinical symptoms for the delayed union lesion. The rate of recurrence of hallux valgus was 6.7% (2/30toes), and infection rate was 0% (0/36 feet). Delayed wound healing rate was 27.8% (10/36 feet), although it recovered at last. Recurrent rate of callosity of plantar side of MTP joint was 0.57% (1/176 toes). [Conclusion] We would suggest that this procedure is a one of the useful procedures in the treatment for forefoot deformities in patients with RA.

## W52-5

### Shortening oblique osteotomy of the metatarsals for lateral toes in rheumatoid arthritis: Mid-term results

Takahiro Netsu, Tadamasu Hanyu  
Department of Rheumatology, Nagaoka Red Cross Hospital

Conflict of interest: None

[Objectives] To clarify the mid-term results of shortening oblique osteotomy of lateral toes in the patients with rheumatoid arthritis. [Methods] Three hundred sixty nine toes of 101 feet in 67 patients in rheumatoid arthritis who had undergone shortening oblique osteotomy of the metatarsals were studied with a minimum two-year follow-up. Dislocation of metatarsophalangeal joint was examined and destructive changes of metatarsal heads were evaluated using Larsen grade. [Results] In pre-operative radiographs, severe dislocations (proximal phalangeal bone dislocated to metatarsal shaft), dislocations, and subluxations were seen in 138 joints (37%), 53 joints (14%) and 52 joints (14%), respectively. Severe destructions of metatarsal heads defined as Larsen IV and V were 81 joints and 26 joints, respectively. At the last follow-up, severe dislocations were observed 4 joints (1%), and two of Larsen V joints were severely dislocated. [Conclusion] There were few cases of recurrent dislocation after shortening oblique osteotomy.

## W52-6

### Short-Medium term result of FINE total ankle arthroplasty in patients with rheumatoid arthritis

Yoshio Nagayama<sup>1</sup>, Akihide Nampei<sup>1</sup>, Hideki Tsuboi<sup>2</sup>, Kenrin Shi<sup>3</sup>  
<sup>1</sup>Department of Orthopaedic Surgery, Osaka Rosai Hospital, Sakai, Japan, <sup>2</sup>Department of Rheumatology, National Hospital Organization Osaka Minami Medical Center, Kawachinagano, Japan, <sup>3</sup>Department of Orthopaedic Surgery and Center for Global Health, Osaka University Hospital, Suita, Japan

Conflict of interest: None

[Objectives] To study Short-Medium term result of FINE total ankle arthroplasty in patients with rheumatoid arthritis. [Methods] Sixteen feet in 15 patients who had undergone aforementioned surgery were studied with minimal follow-up of 1 year. Patient characteristics, JSSF ankle/hindfoot scale, ROM, implant loosening, implant subsidence, and complications were examined. [Results] The average age at the surgery was 65 years. The average follow-up was 43 months. JSSF ankle/hindfoot

scale improved significantly from 37 points preoperatively to 78 at the last follow-up. Average ankle dorsiflexion and plantarflexion changed from 6.7° to 6.0° degrees and 24.3° to 22.7° degrees. There were no significant differences. Two loosening of the tibia components and three subsidence of the talar components were observed. One case removed for revision. The survivorship was 100% at two years and 91% at five years. Two ankle fractures in operation, 2 ankle of delayed wound healing, one ankle of deep infection were observed. [Conclusion] FINE total ankle arthroplasty in patients with rheumatoid arthritis demonstrated generally good Short-Medium term results.

## W53-1

### In vivo knee kinematics for rheumatoid patients after total knee arthroplasty

Shinichiro Nakamura<sup>1,2</sup>, Hiromu Ito<sup>1</sup>, Moritoshi Furu<sup>1</sup>, Richard Komistek<sup>2</sup>, Shuichi Matsuda<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Kyoto University, Kyoto, Japan, <sup>2</sup>Center for Musculoskeletal Research, University of Tennessee, USA, <sup>3</sup>Department of Orthopaedic Surgery, Tamatsukuri Hospital

Conflict of interest: Yes

[Objectives] Previously in vivo knee kinematics has been analyzed for osteoarthritis (OA) patients after total knee arthroplasty. However, it is still unknown for rheumatoid (RA) patients. The purpose of the current study was to determine in vivo three dimensional femoro-tibial kinematics for OA and RA patients. [Methods] Fluoroscopy based in vivo femoro-tibial kinematics of Bi-Surface Knee System was assessed for 12 RA subjects and 54 OA subjects during a deep knee bend activity, using a three dimensional to two dimensional model fitting approach. [Results] Average range of motion was  $120.7 \pm 27.3^\circ$  and  $126.6 \pm 18.9^\circ$  for RA and OA subjects, respectively. The average amount of posterior femoral rollback for the medial condyle was  $6.5 \pm 4.9$  mm and  $9.1 \pm 4.1$  mm for RA and OA subjects, respectively, while the corresponding value for the lateral condyle was  $10.4 \pm 7.1$  mm and  $11.1 \pm 5.0$  mm. The average amount of femoro-tibial axial rotation was  $9.1 \pm 6.2^\circ$  and  $4.9 \pm 6.2^\circ$  for RA and OA subjects, respectively. Significant difference was observed in the amount of axial rotation. [Conclusion] In RA patients, ligament contracture seemed to be less, which might cause greater axial rotation of the femoral component.

## W53-2

### The ACL and PCL in cases of TKA in RA

Mitsuhiro Hariu  
Department of Orthopaedic Surgery, Nihonkai General Hospital

Conflict of interest: None

[Objectives] We have been performing posterior stabilized TKA, but there were reports that pointed out problems related to resected PCL. Reports of Bicruciate-retaining TKA that can be expected normal kinematics of knee beyond cruciate-retaining TKA have been seen recently. So we investigated the rate of intact ACL, PCL inRA and predictive factors for injured ACL. [Methods] This study involved 67 knees in RA who underwent primary TKA. We classified ACL, PCL as intact, frayed and disrupted intraoperatively. The rate of intact ACL, PCL and predictive factors (age, gender, FTA, ROM, Larsen grade, and medical history) for ACL tear were studied. 486 knees in OA were treated as control. [Results] The rate of intact ACL, PCL was 43.3%, 95.5% in RA and 70.2%, 97.6% in OA. OA was statistically higher rate of intact ACL than RA. Larsen grade of injured ACL was significantly greater than one of intact ACL. [Conclusion] These results suggest that about 40% patients who underwent primary TKA in RA might have indication for Bicruciate-retaining TKA.

## W53-3

### Medium term outcome of total knee arthroplasty with autogenous bone graft for tibial defect in patients with rheumatoid arthritis

Kenkou Yamada<sup>1,2</sup>, Shu Saito<sup>1</sup>, Masayuki Seki<sup>1</sup>, Takao Ishii<sup>1</sup>, Gen Suzuki<sup>1</sup>, Shinsuke Kikuta<sup>1</sup>, Manabu Shimizu<sup>1</sup>, Gouki Kinoshita<sup>1</sup>, Takashi Hasegawa<sup>1</sup>, Takanobu Sumino<sup>1,2</sup>, Yasuaki Tokuhashi<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Nihon University School of Medicine, Tokyo, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Itabashi Medical Association Hospital, Tokyo, Japan

Conflict of interest: None

[Objective] Some literature reported about outcomes of TKA with autogenous bone graft for tibial defect. However there were few studies concerning the TKA for rheumatoid arthritis (RA) patients. The purpose of this study was to analyze medium term outcome of TKA with autogenous bone graft fixed by screws for tibial defect in RA patients. [Methods] Fifteen knees of 13 patients traced more than 5-year were registered. Bone graft was performed for the knees accompanied with over 10mm bone defect. The patients consisted of 14 females and 1 male. The mean age at surgery was 60.7 years old, and the mean follow-up period was 7.9 years. Radiological evaluation was performed using femoro-tibial angle (FTA) and bone union. Clinical evaluation was performed using ROM, Knee score, Function score and complications. [Results] The mean FTA improved from 191.1 to 171.8 and all grafted bone were united. The mean knee extension improved from 7.0° to 0°. The mean knee flexion was 120.3° preoperatively, and 116.4° postoperatively. The mean Knee score and Function score improved from 40.2 to 93, and from 35.4 to 76.5, respectively. Infection, loosening and periprosthetic fracture were not recognized. [Conclusion] Autogenous bone graft fixed by screws was also useful in TKA for RA patients.

### W53-4

#### Clinical study of revision total knee arthroplasty for rheumatoid arthritis

Takao Ishii, Shu Saito, Takanobu Sumino, Gen Suzuki, Manabu Shimizu, Gouki Kinoshita, Kenkou Yamada, Takashi Hasegawa, Yasuaki Tokuhashi  
Department of Orthopaedic Surgery, Nihon University School of Medicine, Tokyo, Japan

Conflict of interest: Yes

[Objectives] We report 24 cases 31 knees revision TKA done in our units. [Methods] 31 revision TKA procedures were performed and observed over 1 year; 4 of these were performed on men and 27 on women. The average age of the primary TKA procedures was 52.8 years. [Results] The mean interval from initial surgery to revision TKA was 9.9 years (range, 2 years-22 years). The most common reasons for failure were loosening (11 knees), ultra-high molecular weight polyethylene (UHMWPE) wear (8 knees), instability (7 knees), infection (3 knees), and metallosis by metal backed patella (3 knees). The operative methods were isolated polyethylene insert exchange (8 knees), isolated patella components exchange (3 knees). In other 20 cases, reimplantation was performed after component removal.

### W53-5

#### Total Knee Arthroplasty in Rheumatoid Arthritis with Biologic's Therapy-Comparison between Arthroplasty before Biologic Therapy and Biologic Therapy before Arthroplasty-

Takanobu Sumino, Shu Saito, Takao Ishii, Yasuaki Tokuhashi  
Department of Orthopaedic Surgery, School of Medicine, Nihon University, Tokyo, Japan

Conflict of interest: None

**Introduction:** The objective of this study was to demonstrate clinical outcome between Surgery before Biologic and Biologic before Surgery for Total knee Arthroplasty (TKA). **Materials and Methods:** Thirty patients were the subject of the study. There were 39 joints in Arthroplasty before Biologic (AB group) and 31 joints in Biologic before Arthroplasty, respectively. We estimated the patients characteristics, the laboratory data, the clinical outcomes, DAS 28 and complications after surgery. **Results:** No significant difference was noted in the patients characteristics, the clinical outcomes, DAS 28. Conversely, post operative knee range of motion in BA group have a significant better than AB group (P<0.05). There was one deep infection in AB group. In BA group, three were the superior infections. **Discussion and Conclusion:** This study showed that Biologics before arthroplasty group supposed to be more effective in the

postoperative knee motion and the perioperative care than Arthroplasty before biologics group.

### W53-6

#### Application of contrast-enhanced computed tomography for detecting venous thromboembolism after total hip arthroplasty in rheumatoid arthritis patients

Junichi Okamoto<sup>1</sup>, Yuya Takakubo<sup>1</sup>, Daiichiro Takahara<sup>1</sup>, Suran Yang<sup>1</sup>, Yasushi Naganuma<sup>1</sup>, Tomoyuki Hirayama<sup>1</sup>, Akiko Sasaki<sup>1</sup>, Kan Sasaki<sup>1</sup>, Hiroshi Oorui<sup>2</sup>, Michiaki Takagi<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Yamagata University School of Medicine, <sup>2</sup>National Hospital Organization Yamagata Hospital

Conflict of interest: None

[Objective] We investigated the venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary thromboembolism (PE) detected by contrast-enhanced computed tomography (CT) scanning in rheumatoid arthritis (RA) patients after total hip arthroplasty (THA). [Method] We analyzed all RA patients after the surgery of THA for detecting VTE by CT scanning since April 2013 (CT group) compared to control group (DD group). DD Group applied contrast-enhanced CT for RA patients when their value of D-dimer test was over 20 ng/ml after their THA. [Result] CT and DD group included both ten hips. Two DVT and two PE were detected by CT scanning in CT group, but not in DD group. In any cases of DD group, CT scanning was not performed, because the value of D-dimer test was under 20 ng/ml, which we applied as the standard value for ordering contrast-enhanced CT scanning. The mean values of D-dimer were 7.2 ng/ml and 6.6 ng/ml on the 6th day after their THA, respectively. [Conclusion] CT scanning was detected VTE in 40% RA patients (4/10) after THA, however no findings in DD group. It might be required to apply CT scanning for detecting VTE in all RA patients after THA, while possible risk for missing asymptomatic VTE in DD group is taken into account.

### W54-1

#### Sustainability of Efficacy of Etanercept After Several Repetitions of Start and Stop -RESUME study-

Kentaro Inui<sup>1</sup>, Tatsuya Koike<sup>2,3</sup>, Masahiro Tada<sup>1</sup>, Yuko Sugioka<sup>1,2</sup>, Kenji Mamoto<sup>1</sup>, Tadashi Okano<sup>1</sup>, Akira Sakawa<sup>4</sup>, Kenzo Fukushima<sup>5</sup>, Hiroaki Nakamura<sup>1</sup>

<sup>1</sup>Orthopaedic Surgery, Osaka City University Graduate School of Medicine, <sup>2</sup>Center for Senile Degenerative Disorders, Osaka City University Graduate School of Medicine, <sup>3</sup>Search Institute for Bone and Arthritis Disease, Shirahama Hamayu Hospital, <sup>4</sup>Orthopaedic Surgery, Osaka City Juso Hospital, <sup>5</sup>Orthopaedic Surgery, Fujiidera Municipal Hospital

Conflict of interest: None

**Objective:** In daily practice, some RA patients cannot afford treatment with bDMARDs (BIO). One of the way to reduce cost is that its use is limited only when disease activity (DA) is high. However, flare-up is of concern in discontinuation of BIO and its efficacy is not always assured when restarting the same BIO. We conducted a study using etanercept (ETN) as needed only in high DA. **Methods:** BIO-naive RA patients with DA of DAS28 $\geq$ 3.2 were enrolled. ETN (50 mg/week) was administered until DAS28<3.2 was achieved. ETN was then discontinued and the patients were observed every 2 months. If DA recurred, ETN was administered again. This strategy of repetition of start and stop was maintained for 2 years. **Results:** Of the 31 patients enrolled in this study, 11 were received ETN throughout the study period and 7 had no flare-up of DA after ETN discontinuation. In the remaining 13 the strategy of start & stop was maintained. In those 13 cases LDA was achieved at the end of study period. Cost saving was about 28%. Structural damage evaluated by mTSS was found in half of those. **Conclusion:** We confirmed that the efficacy of ETN was sustained after repetition of start & stop, however, structural damage progressed in half of those.

### W54-2

#### Review of Bio free remission in rheumatoid arthritis (RA)

Shiro Ohshima, Masato Matsushita, Soichiro Tsuji, Yoshinori Harada,

Eriko Tanaka, Maiko Yoshimura, Satoru Teshigawara, Akiko Yura, Takuro Nii, Takashi Shimizu, Shigeyoshi Tsuji, Hideki Tsuboi, Shosuke Akita, Jun Hashimoto, Yukihiko Saeki  
NHO Osaka Minami Medical Center

Conflict of interest: None

[Objectives] The rate of bio-free remission was assessed in RA patients who discontinued biologics (bio) for RA after achieving clinical remission. [Methods] RA patients were treated with bio, and if patients were fulfilled our criteria of remission (DAS28ESR<2.6, and the dose of prednisolone $\leq$ 5mg/day) for over at least 6 months, they discontinued bio. If they were still fulfilled the remission criteria 1 year after discontinuation of bio, we define them as bio-free remission. [Results] Of 41 patients treated with bio, 21 patients achieved bio-free remission 1 year after discontinuation. The characteristics of RA patients in the group of achieving bio-free remission (BFRG) were as follows, mean age 52.7y; female 67%; mean RA duration 5.8y (duration<3y 42.9%); DAS28ESR 1.9; MMP-3 58.7ng/ml the normalization rate of MMP-3 86.7%. Moreover, in 6 patients, the titers of RF were normalized during the treatment of bio, and the titer of RF declined in all BFRG. [Conclusion] Our result suggested that factors contributing to 1 year maintenance of bio-free remission include the normalization or improvement of the titer of RF. Moreover, it is considered the achievement of deeper remission in early stage of RA also contribute to the maintenance of bio-free remission.

### W54-3

#### Discontinuation of infliximab after attaining remission in patients with rheumatoid arthritis- long term clinical results

Kaori Kobori, Makoto Kobori  
Kobori Orthopaedic Clinic

Conflict of interest: None

[Objectives] Reports about discontinuation of infliximab (IFX) after attaining remission in patients with rheumatoid arthritis are rare. We report long term our clinical results about it. [Methods] From Oct.2004 to Sept.2014, 86 RA patients were treated with IFX in our clinic. In 86 patients, 29 patients achieved to remission and discontinued IFX after 6months keeping remission with only MTX. Remission is Boolean with normal MMP3 [Results] We followed them for average 52months. Background of 29 patients are 5males, 24females, caused RA average 6years including 14 patients of early RA. During our following, 21 patients (72%) keep remission. 8 patients had recurrence: 2 cases within 1 year, 3 cases within 2 years, 3 cases over 3 years. [Conclusion] Our clinical results 72% for average 52 months is better than RRR study (55% for 1 year). Because of our remission is more strict and our patients include 14 early RA patients. We need longer following after remission because of recurrence over 3 years.

### W54-4

#### The remission sustainability of the newly inducted patients by biologics usage. - From NinJa Database-

Jinju Nishino<sup>1</sup>, Yuho Kadono<sup>2</sup>, Toshihiro Matsui<sup>3</sup>, Tetsuro Yasui<sup>2</sup>, Naoko Shoda<sup>2</sup>, Yasunori Omata<sup>2</sup>, Takuma Koyama<sup>2</sup>, Kumiko Ono<sup>1</sup>, Hiroyuki Oka<sup>5</sup>, Sakae Tanaka<sup>2</sup>, Shigeto Tohma<sup>4</sup>

<sup>1</sup>Department of Orthopaedic Surgery, The University of Tokyo Hospital, <sup>2</sup>Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, <sup>3</sup>Department of Rheumatology, Sagami Hospital Hospital, National Hospital Organization, <sup>4</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami Hospital Hospital, National Hospital Organization, <sup>5</sup>22nd Century and Research Center, The University of Tokyo Hospital

Conflict of interest: None

[Objectives] The aim of this study is to evaluate of remission sustainability of the newly inducted patients by biologics usage. [Methods] 106 rheumatoid arthritis patients newly inducted remission by biologics were extracted from 2011 National database of Rheumatic disease by iR-net (NinJa). They followed for 2 years. Disease activity, physical condition and treatment changes were investigated. [Results] The survival rate was

69.0%% at 2012 and 63.5%% at 2013. Deep remission patients (DAS-28ESR<1.6) presented better survival rate. Trial of Bio-free resulted failure, 65.6% re-started biologics usage. the quarter of patients need treatment augmentation by MTX or Corticosteroid.

### W54-5

#### Condition factors affecting discontinuation of Adalimumab treatment after meeting criterion of drug holidays

Toshihiko Hidaka<sup>1</sup>, Eiko Nishi<sup>1</sup>, Shota Sakaguchi<sup>1</sup>, Yasufumi Kai<sup>1</sup>, Hiroshi Kuroda<sup>1</sup>, Yayoi Hashiba<sup>2</sup>, Kazuyoshi Kubo<sup>2</sup>, Yasuhiro Nagatomo<sup>2</sup>, Akihiko Okayama<sup>2</sup>

<sup>1</sup>Institution of Rheumatology, Zenjinkai Shimin-no-Mori Hospital, Miyazaki, Japan, <sup>2</sup>Department of Rheumatology, Infectious Disease and Laboratory Medicine, University of Miyazaki, Internal Medicine, Miyazaki, Japan

Conflict of interest: Yes

[Objective] We investigated the condition factors affecting discontinuation of Adalimumab (ADA) in patients with rheumatoid arthritis (RA) after meeting criterion of drug holidays. [Methods] Sixty-four patients (11 males and 53 females, mean age; 59 years) treated with ADA were examined. When patients who were administered ADA for at least 1 year sustained remission for  $\geq$ 6 months and desired to discontinue ADA, ADA was discontinued. We compared the patient backgrounds between the group of discontinuation of ADA (group A) and that of continuation of ADA (B group) after meeting criterion of drug holidays. [Results] Twenty-four (38%) of 64 patients fulfilled a criterion of drug holidays for ADA, 14 patients (22%) discontinued ADA after due to remission, and 10 patients (16%) continued ADA. Compared with group B, average disease duration at the initiation of ADA (A; 53 months vs. B; 120 months,  $p<0.01$ ) and mean total treatment duration by ADA (A; 21 months vs. B; 53 months,  $p<0.001$ ) was significantly short. [Conclusion] Among the patients meeting criterion of drug holidays for ADA, disease duration of patients who wanted to stop ADA were shorter than those who did not want to. Then, treatment period of the former was shorter than latter.

### W54-6

#### The rate of successful withdrawal of biologics in rheumatoid arthritis patients with inadequate response to methotrexate or leflunomide

Taio Naniwa<sup>1,3</sup>, Mikiko Kajiura<sup>3</sup>, Shinya Tamechika<sup>2</sup>, Shinji Maeda<sup>2</sup>, Akio Niimi<sup>2</sup>

<sup>1</sup>Early Arthritis Clinic, Division of Respiratory Medicine, Allergy and Rheumatology, Nagoya City University Hospital, <sup>2</sup>Division of Respiratory Medicine, Allergy and Rheumatology, Nagoya City University Hospital, <sup>3</sup>Rheumatology Clinic, Takeuchi Orthopedics & Internal Medicine

Conflict of interest: Yes

[Objectives] To assess the rate of successful withdrawal of biologics in patients with RA and an inadequate response to MTX or leflunomide (LEF). [Methods] Consecutive patients who were treated by the lead author and started biologics for active RA despite MTX or LEF treatment from Jan 2004 to Oct 2013 were analyzed in terms of the rates of achieving biologic- and oral glucocorticoid-free remission for 6 and 12 months. Remission was defined as any one of the following definitions was satisfied; ACR/EULAR remission criteria, DAS28-ESR  $\leq$ 2.6, or DAS28-CRP  $\leq$ 2.3. [Results] A total of 123 patients could be analyzed, in whom 113, 8, and 2 were initially treated with a TNF inhibitor, tocilizumab, and abatacept, respectively. The number of patients who were withdrawn from biologics after achieving remission was 71 (58%). The rates of successful withdrawal from biologics for 6 and 12 months were 56/64 (88%) and 38/50 (76%), and biologics used just before remission for 6 months and 12 months were a TNF inhibitor in 54 and tocilizumab in one, and a TNF inhibitor in 38, respectively. [Conclusions] Successful withdrawal of biologics after achieving remission is realistic target in a substantial number of recent-onset RA patients. TNF inhibitors are key biologics to achieve this goal.

## W55-1

### Evaluation of the efficacy and safety of 7 biologics as first line treatment in RA - from data of 2129 patients with RA at University of Occupational and Environmental Health -

Yoshino Inoue, Kazuyoshi Saito, Kazuhisa Nakano, Shingo Nakayamada, Shunsuke Fukuyo, Satoshi Kubo, Ippei Miyagawa, Shintaro Hirata, Yoshiya Tanaka

The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

Conflict of interest: None

[Objective] The aim of study was to evaluate the efficacy of 1<sup>st</sup> biologics in daily clinical practice in RA [Methods] Baseline characteristics of 1713 patients who received biologics after July in 2008 at our institute and their efficacy were evaluated. [Results] Patients were treated with IFX330, ETN229, ADA296, TCZ123, ABT135, GLM20 as first line biologics. Patients with a short disease duration and low HAQ were preferentially treated with IFX and ADA. We tended to choose ETN for the treatment to elderly patients. TCZ was administered to the patients with high titers of ESR, CRP and MMP-3. SDAI remission was achieved in patients treated with IFX44%, ADA47%, GLM47%, ETN26%, TCZ26%, ABT30%. Bio-free remission was obtained at the percentage of IFX22%, ADA10%, GLM5%. There was no difference among treatment groups regarding the retention rate at 1 year. [Conclusions] All treatment groups as first line had significant improvements of SDAI and resulted in the good retention rate. Anti-TNF antibodies bought about higher induction rate of SDAI remission as well as bio-free remission. The present data imply us that TCZ showed high efficacy even in the patients with high titer of ESR, CRP, and ETN was tended to administer to elderly patients without discontinuation due to adverse events.

## W55-2

### Study of the presence of autoantibodies in rheumatoid arthritis patients treated with TNF inhibitors

Ran Matsudaira<sup>1</sup>, Naoto Tamura<sup>2</sup>, Nagachika Sugisaki<sup>2</sup>, Tomoko Ito<sup>2</sup>, Kentaro Minowa<sup>2</sup>, Michihiro Ogasawara<sup>2</sup>, Ken Yamaji<sup>2</sup>, Yoshinori Kanai<sup>1</sup>, Kenjiro Yamanaka<sup>1</sup>, Yoshinari Takasaki<sup>2</sup>

<sup>1</sup>Division of Internal Medicine and Rheumatology, Sasaki Institute Kyoundo Hospital, <sup>2</sup>Internal Medicine and Rheumatology, Juntendo University, School of Medicine

Conflict of interest: None

[Objectives] To study the presence of autoantibodies in rheumatoid arthritis (RA) patients treated with TNF inhibitors. [Methods] We examined 246 RA patients treated with TNF inhibitors as the first biologics DMARDs: infliximab (IFX); 116, etanercept (ETN); 64, adalimumab (ADA); 36, and golimumab (GLM); 30 and studied the presence of anti-nuclear antibodies (ANA) and anti-dsDNA antibodies (anti-DNA) before and after treatment. We compared the positive rate of anti-DNA between anti-Ro/SS-A (anti-Ro)-positive and -negative patients. ANA levels  $\times 40$  was considered positive. Anti-DNA levels  $> 6.0$  IU/ml was considered positive. [Results] The positive rate of ANA before and after treatment with IFX, ETN, ADA, and GLM were 64.7% to 89.7%, 56.3% to 68.8%, 72.2% to 77.8%, and 66.7% to 60.0%, respectively. Anti-DNA increased from baseline after treatment with IFX, ETN, ADA, and GLM (4.3% to 40.5%, 1.6% to 10.9%, 11.1% to 25.0%, and 0.0% to 3.3%, respectively). Moreover, the positive rate of anti-DNA in patients treated with IFX and ADA was notably increased in anti-Ro-positive patients compared to anti-Ro-negative patients (68.2% vs 36.2%;  $p=0.007$ , 66.7% vs 13.3%;  $p=0.039$ , respectively). [Conclusion] The presence of autoantibodies in patients treated with GLM was low compared to IFX and ADA.

## W55-3

### Response to biologics in anti-SS-A antibody positive patients with rheumatoid arthritis

Shinya Hagiwara, Hiroto Tsuboi, Hidenori Takahashi, Mizuki Yagishita, Saori Abe, Yuko Kurashima, Shunta Kaneko, Hoshimi Kawaguchi, Hiroyuki Takahashi, Hiroshi Ebe, Masahiro Yokosawa, Hiromitsu Asashima, Tomoya Hirota, Naoto Umeda, Yuya Kondo, Hiroshi Ogishima, Takeshi Suzuki, Isao Matsumoto, Takayuki Sumida

Department of Internal Medicine, Faculty of Medicine, University of Tsukuba

Conflict of interest: None

[Objectives] To clarify the response to three different biologics (Bio) in anti-SS-A antibodies positive patients (Pts) with RA. [Methods] We targeted Bio naïve RA who started administration of Bio, and were examined for anti-SS-A Ab in our department between Dec 2003 and Mar 2014. For these Pts treated with infliximab (IFX), tocilizumab div (TCZ), and abatacept div (ABT), we examined 1) presence of anti-SS-A Ab and complication of Sjögren's syndrome (SS), and 2) change in DAS28-CRP from baseline (0W) to 54W, retrospectively. [Results] 1) Among 74 Pts treated with IFX, 9 Pts were anti-SS-A Ab positive (2 with SS), other 65 Pts were negative (0 with SS). For 26 Pts with TCZ, 5 were positive (1 SS), 21 were negative (0 SS). For 13 Pts with ABT, 9 were positive (9 SS), 4 were negative (4 SS). 2) For IFX, DAS28-CRP decreased from  $4.3 \pm 1.1$  (0W) to  $3.9 \pm 1.6$  (54W) ( $P=0.36$ ) in anti-SS-A Ab positive Pts, and from  $4.1 \pm 1.0$  to  $2.6 \pm 1.1$  ( $P<0.01$ ) in negative Pts. For TCZ, it decreased from  $4.6 \pm 1.4$  to  $1.8 \pm 0.6$  ( $P=0.01$ ) in positive Pts, and from  $4.2 \pm 1.1$  to  $2.0 \pm 0.7$  ( $P<0.01$ ) in negative Pts. For ABT, it decreased from  $3.5 \pm 1.1$  to  $2.8 \pm 1.4$  ( $P=0.07$ ) in positive Pts, and from  $3.3 \pm 0.5$  to  $1.7 \pm 0.7$  ( $P=0.04$ ) in negative Pts. [Conclusion] Anti-SS-A Ab positive RA might be resistant to IFX, while responsive to TCZ and ABT.

## W55-4

### Efficacy of Bio switch in RA patients

Akiko Sato, Hiroshi Nakamura, Kenji Takahashi, Kenji Takenouchi, Hidemi Kawaji, Shinro Takai

Orthop. Surg., Nippon Medical School. Graduate School of Medicine

Conflict of interest: None

[Objectives] The purpose of this study is to investigate the efficacy of switching biologics in RA patients who were irresponsive to other biologics. [Methods] We investigated outcome of switching prior biologics to ETA, ADA, GOL, TOC, ABT in November 2014. [Results] The numbers of cases switching to each biologics were as follows; ETA: 64 cases, ADA: 12 cases, GOL 10 cases, TOC: 31cases, ABT: 24 cases. The numbers of cases that continued switched agents were 10 (15.6%), 5 (41.6%), 6 (60%), 10 (41.7%), 7 (31.8%), respectively. The persistency rates from a TNF inhibitor to another TNF inhibitor, from a TNF inhibitor to TOC and from a TNF inhibitor to ABT were 27.5%, 66.6% and 60% respectively ( $p<0.05$ ). The efficacy of multi-switching was inferior to the first switch. [Conclusion] The most effective switching from a TNF inhibitor was switching to TOC and switching to ABT was the second.

## W55-5

### The effectiveness of 2nd TNF inhibitors or non-TNFIs in refractory rheumatoid arthritis

Takayoshi Owada, Kazuhiro Kurasawa, Ayae Tanaka, Ryutaro Yamazaki, Harutsugu Okada, Satoko Arai, Reika Maezawa

Department of Pulmonary Medicine and Clinical Immunology, Dokkyo Medical University

Conflict of interest: None

[Objectives] To clarify factors which influence the effectiveness of 2nd TNF inhibitors (TNFIs) or non-TNFIs in rheumatoid arthritis (RA) resistant to initial biologics. [Methods] RA patients refractory to initial biologics with switching to 2nd ones were enrolled in this study, in whom clinical background, disease activity and therapy before switching were examined. Patient with DAS28-CRP $<2.7$  in addition to continuation for one year was classified as responder. [Results] 2nd biologics achieved to DAS28-CRP $<2.7$  in addition to continuation for one year in 31.4% of 35 RA patients with switching from initial TNFI to 2nd TNFI (TNFI $\rightarrow$ TNFI), in 25.0% of 12 with TNFI $\rightarrow$ non-TNFI and in 50.0% of 6 with non-TNFI $\rightarrow$ TNFI. In patients with switch of TNFI $\rightarrow$ TNFI, responders had significantly higher rate of methotrexate $\geq 8$ mg/week than non-responders (90.9% vs 41.7%), and significantly higher rate of ACPA- or RF-negative RA (ACPA; 66.7% vs 100.0%, RF; 40.0% vs 4.17%). There were no differences in clinical background, disease activity and

therapy between responders and non-responders with switch of TNFI→non-TNFI, and with non-TNFI→TNFI. [Conclusion] Effectiveness of 2nd biologics was similar in TNFI and non-TNFI. But in switch of TNFI→TNFI, clinicians must pay attention to MTX dosage and ACPA/RF-negative.

### W55-6

#### Temporal Changes Analyses of Biological Usages from DPC data of National University Hospitals

Katsuhiko Takabayashi

Department of Medical Informatics, Chiba University, Chiba, Japan

Conflict of interest: None

[Objectives] To analyze monthly change of biological usages from DPC data of national university hospitals called CISA. [Methods] We collected the DPC data of 13 national university hospitals to CISA project. We chose the data of RA patients and analyzed the drugs administered to each patient. The period of analysis was from October 2005 when biological treatment started until May, 2014. [Results] In May 2014, total usage of the month was 2431. Tocilizumab is the most used 669cases: 27.5%) and second was etanercept (441cases: 18.1%), third was infliximab (385 cases: 15.8%), followed by adalimumab and abatacept. New patients started in month have been gradually increasing except first two months and now about 5% of the patients were new ones. All biologicals except tocilizumab seem to be almost equilibrium state at the moment. DMARDs and MTX treatment were compared according to the hospital but the results depend on universities. [Conclusion] We showed that we can see the monthly changes of biological usage and other drugs in RA patients at a glance from DPC data.

### W56-1

#### Examination about the influence that Abatacept *div* (ABT) treatment start time in rheumatoid arthritis (RA) patient of MTX inadequate response (MTX-iR) and biologics naïve (bio-naïve). - multicenter, prospective study-Can we select Abatacept for RA patients as 1st biologic? (ORIB Study)

Takafumi Hagiwara<sup>1</sup>, Tomoko Nakamura<sup>2</sup>, Hajime Owaki<sup>3</sup>, Masataka Nishikawa<sup>3</sup>, Akira Okamoto<sup>4</sup>, Takako Miura<sup>5</sup>, Koji Fukuda<sup>6</sup>, Yoshitada Sakai<sup>7</sup>, Mitsuo Namiki<sup>8</sup>, Kazuya Kamada<sup>1</sup>, Momo Maruoka<sup>1</sup>, Tsukasa Matsubara<sup>5</sup>

<sup>1</sup>Department of Rheumatology, Takarazuka City Hospital, Takarazuka, Japan, <sup>2</sup>Department of Rheumatology, Hyogo Rehabilitation Centre Central Hospital, Kobe, Japan, <sup>3</sup>Department of Orthopaedic Surgery, Japan Community Health Care Organization Osaka Hospital, Osaka, Japan, <sup>4</sup>Rheumatology, National Hospital Organization Himeji Medical Center, Himeji, Japan, <sup>5</sup>Rheumatic Disease Center, Matsubara Mayflower Hospital, Kato, Japan, <sup>6</sup>Department of Orthopaedic Surgery, Kakogawa West City Hospital, Kakogawa, Japan, <sup>7</sup>Division of Rehabilitation Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, <sup>8</sup>Namiki Clinic, Takarazuka, Japan

Conflict of interest: None

[Objectives] In the treatment strategy of RA, all biologics are put same positioning by their curative effect and joint destruction prevention effect. We planned multicenter, single arm, prospective clinical study to find out a treatment strategy of RA promoted efficiency. And, we examined the influence that time to biologic intervention gave for curative effect. [Methods] We enrolled 29 RA patients who started ABT *div* in higher than moderate disease activity of MTX-iR and bio-naïve. We examined the disease activity score, mHAQ, MMP-3 until 48wks. And then, we inspected the influence that a factor, such as disease duration and ACPA, gave for curative effect. [Results] The clinical remission achievement rate at the time of 24 wks from ABT induction, respectively, was as follows. DAS28CRP; 34.5%, DAS28ESR; 24.1%, SDAI; 20.7%, CDAI; 20.7%. We compared the introduction periods more than 12Mo with under 12Mo. We found improvement of the disease activity evaluation after treatment induction 24wks later, and recognized improvement with statistical significant difference in the group which performed start of therapy by 12 months. [Conclusion] We indicated that we could get a higher clinical effect by starting ABT to the rheumatic until onset 12

months of the rheumatoid arthritis.

### W56-2

#### Examination of the efficacy and predictive factors of clinical remission at 48 weeks after treatment with abatacept in bio-naïve patients with rheumatoid arthritis (RA)

Masahiro Sekiguchi<sup>1,2</sup>, Takao Fujii<sup>2</sup>, Masayasu Kitano<sup>1,2</sup>, Kiyoshi Matsui<sup>1,2</sup>, Hideo Hashimoto<sup>2</sup>, Akira Yokota<sup>2</sup>, Kenji Miki<sup>2</sup>, Aihiro Yamamoto<sup>2</sup>, Takashi Fujimoto<sup>2</sup>, Toshihiko Hidaka<sup>2</sup>, Naoki Shimmyo<sup>2</sup>, Keiji Maeda<sup>2</sup>, Hideko Nakahara<sup>2</sup>, Takanori Kuroiwa<sup>2</sup>, Ichiro Yoshii<sup>2</sup>, Shigeo Irimajiri<sup>2</sup>, Yoshio Ozaki<sup>2</sup>, Takao Takeuchi<sup>2</sup>, Motomu Hashimoto<sup>2</sup>, Masao Tanaka<sup>2</sup>, Yuji Nozaki<sup>2</sup>, Kenshi Higami<sup>2</sup>, Kosaku Murakami<sup>2</sup>, Koichiro Ohmura<sup>2</sup>, Yutaka Kawahito<sup>2</sup>, Norihiro Nishimoto<sup>2</sup>, Tsuneyo Mimori<sup>2</sup>, Hajime Sano<sup>1,2</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan, <sup>2</sup>ABROAD Study Group

Conflict of interest: Yes

[Objectives] To assess the efficacy and predictive factors of SDAI clinical remission (CR) at 48 weeks after treatment with abatacept in bio-naïve patients with rheumatoid arthritis (RA). [Methods] We evaluated in 272 RA patients (mean age; 61.8 yrs, mean disease duration; 8.1 yrs, mean SDAI; 24.6) enrolled in the ABROAD study who were treated with abatacept at least 48 weeks. The efficacy was evaluated by CR rate (SDAI ≤ 3.3) at 48 weeks after treatment. Using the univariate and multivariate logistic regression analysis, we evaluated predictive factors of CR in the baseline, 12, or 24 weeks after treatment, respectively. The cut-off values of each variable were extracted from ROC curve. [Results] SDAI CR rate was 27.2%. Predictive factors of CR were as follow: disease duration, DAS28CRP score and HAQ score at baseline, sex (male>female), DAS28CRP score and HAQ score at 12 weeks, DAS28CRP score and HAQ score at 24 weeks. The cut-off values of each variable were as follow: disease duration was 5.7 years, DAS28CRP score was 4.1, 2.5 or 2.4 at 0, 12 or 24 weeks, respectively. HAQ score was 0.75, 0.375 or 0.375 at 0, 12 or 24 weeks, respectively. [Conclusion] DAS28CRP and HAQ could become predictive factors of the SDAI remission.

### W56-3

#### High serum level of haptoglobin is associated with the response of 24 weeks abatacept therapy in conventional DMARDs non-respondering rheumatoid arthritis patients

Takahiro Yoshikawa, Kiyoshi Matsui, Kota Azuma, Chie Ogita, Takeo Abe, Yuichi Yokoyama, Tetsuya Furukawa, Takuya Hino, Atsushi Saito, Aki Nishioka, Masahiro Sekiguchi, Naoto Azuma, Shinichiro Tsunoda, Hajime Sano

Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine

Conflict of interest: None

[Objectives] To investigate whether serum levels of haptoglobin (Hpg) are associated with the response of abatacept (ABT) 24 weeks therapy in patients not responding to cDMARDs. [Methods] 36 active Bio-naïve RA patients in patients not responding to cDMARDs were treated with ABT. Clinical variables are assessed at week 0, 12 and 24, and serum levels of Hpg levels were tested at week 0 and week 12. After 24 weeks of treatment, the patients were categorized as responders (week 24 SDAI ≤ 11) and non-responders (all others). [Results] After 24 weeks of ABT treatment, 58.3% of RA patients were categorized as responders. In univariate and multivariate analysis, Hpg < 130 mg/dl at baseline is significant independent factor for responders (odds ratio 6.044 and 6.37, both P<0.05) at week 24. Interestingly, in patients with baseline Hpg < 130mg/dL, responder rate of those whose Hpg change ≥ 20% at week 12 is 80%, but in patients with baseline Hpg ≥ 130mg/dL, responder is none whose serum Hpg change < 20%. [Conclusion] High serum levels of Hpg at baseline are associated with inadequate response of 24 weeks ABT treatment in cDMARDs-nonresponding RA patients. Further replication studies in larger samples are needed to validate Hpg as a potential predictive biomarker for response to ABT therapy in RA.

## W56-4

### Efficacy and safety of abatacept for treating rheumatoid arthritis: Kagoshima Abatacept Registry

Masaki Akimoto<sup>1,2</sup>, Takemasa Matsuda<sup>1,3</sup>, Hideo Ohtsubo<sup>1,3</sup>, Noriko Aoki<sup>1,3</sup>, Tomoe Kaieda<sup>1,3</sup>, Sanae Shigemizu<sup>1,3</sup>, Tamami Yoshitama<sup>1,4</sup>, Nobutaka Eiraku<sup>1,5</sup>, Kunihiro Kodama<sup>1,6</sup>, Tomomaro Izumihara<sup>1,7</sup>

<sup>1</sup>Kagoshima Abatacept Study Group, <sup>2</sup>Department of Hematology and Immunology, Kagoshima University Hospital, <sup>3</sup>Center for Rheumatic Diseases, Japanese Red Cross Kagoshima Hospital, <sup>4</sup>Yoshitama Rheumatology and Internal Medicine Clinic, <sup>5</sup>Eiraku Internal Medicine Clinic, <sup>6</sup>Yonemori Hospital, <sup>7</sup>Izumihara Rheumatology and Internal Medicine Clinic

Conflict of interest: None

[Objectives] To evaluate the efficacy and safety of abatacept (ABT) in patients with rheumatoid arthritis (RA). [Methods] The present study involved the collaboration of 5 institutions. We assessed the efficacy and safety of ABT 1 year after its initial administration in 129 patients with RA. [Results] A total of 115 women and 14 men with a mean baseline age and disease duration of 60.6 and 11.0 years, respectively, were enrolled. The mean baseline DAS28-CRP and HAQ score were 4.32 and 1.32, but decreased significantly at 1 year to 3.23 ( $p < 0.0005$ ) and 1.04 ( $p < 0.01$ ), respectively. The percentages of remission, low, moderate, and high disease activity at 1 year were 26.4%, 14.0%, 30.2%, and 29.5%, respectively. Logistic regression analysis revealed a significant association between remission at 1 year and the number of biologics used previously, Steinbrocker stage, and baseline DAS28-CRP score. Adverse events and infection occurred in 33.3% and 24.8% of patients, respectively. The prevalence of infection was increased in patients with a long disease duration, advanced disease stage, and no MTX use. Age, interstitial pneumonia, and COPD were not found to be correlated with infection. [Conclusion] These findings provide some insight into the beneficial use of ABT for treating RA.

## W56-5

### Assessing Factors Associated with Efficacy of Abatacept on Patients with Rheumatoid Arthritis –SWEET Cohort

Misuzu Yamashita<sup>1</sup>, Masamitsu Natsumeda<sup>1</sup>, Koji Takasugi<sup>1</sup>, Kazuhiko Ezawa<sup>1</sup>, Yoshihisa Nasu<sup>2</sup>, Wataru Yamamoto<sup>3</sup>, Keiichiro Nishida<sup>4</sup>

<sup>1</sup>Department of Internal Medicine, Center of Rheumatology, Kurashiki Sweet Hospital, Kurashiki, Japan, <sup>2</sup>Department of Orthopedic, Center of Rheumatology, Kurashiki Sweet Hospital, Kurashiki, Japan, <sup>3</sup>Department of Clinical Information Management, Kurashiki Sweet Hospital, Kurashiki, Japan, <sup>4</sup>Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Conflict of interest: None

[Objectives] Predictive factors for clinical response to Abatacept (ABT) are examined for patients with Rheumatoid Arthritis (RA). Considered factors include autologous antibodies and clinical baseline. [Methods] 48 RA patients treated with ABT through Oct 2010 to Aug 2012 are subjects for analysis, which divided in two groups by means of RF, anti-CCP (ACPA), MMP-3, disease activity (DA), and concomitant use of MTX. Evaluations by 104 weeks are made in following items; drug retention rate, DAS response, remission rate, and  $\Delta$ TSS. [Results] No significant association was found in RF. High ACPA and high baseline DA are significantly associated with DAS response at week 52 as well as at week 104 for high baseline DA group. Progression of TSS is significantly high in patients with high MMP-3, similar trend was also found in groups with high RF or high ACPA, which gives discrepancy between radiographic and clinical response. Concomitant use of MTX showed significant association with lower DAS28-ESR, greater remission rate, and less radiographic progression. [Conclusion] It should follow T2T approach for patients with high in RF, ACPA, and MMP-3 to consider radiographic progression, therefore concomitant MTX is desired for the patients with ABT if they can tolerate.

## W56-6

### Short-term results of abatacept for biologic-naive patients with rheumatoid arthritis

Tomoko Tomita, Miyuki Bohgaki, Hideki Kasahara, Takao Koike  
Department of Rheumatology, NTT Sapporo Medical Center, Sapporo, Japan

Conflict of interest: None

[Objectives] To clarify the efficacy and safety of abatacept (ABT) for biologic-naive patients with rheumatoid arthritis (RA). [Methods] Biologic-naive patients with RA treated with ABT from June 2011 to November 2014 were included. We analyzed retrospectively the characteristics and adverse events, concurrent drugs, and disease activity. Disease activity was assessed using DAS28-ESR and EULAR response at weeks 4, 12, 24 and 48. [Results] Twenty-three biologic-naive patients were treated with ABT. The mean age and the mean disease duration, the mean duration of administration was 68.6 years old, 6.1 years, 15.1 months, respectively. Ten patients took prednisolone (mean 3.9mg/day) and 16 patients took methotrexate (mean 6.7mg/week). These patients had many complications (7 interstitial pneumonia, 5 cancers, 17 infections, 9 chronic kidney diseases). Only one patient discontinued because of adverse event of infection. DAS28-ESR scores were  $5.0 \pm 1.1$ ,  $3.9 \pm 0.9$ ,  $3.5 \pm 1.5$ ,  $3.3 \pm 1.5$  and  $3.0 \pm 1.7$  at weeks 0, 4, 12, 24 and 48. EULAR good and moderate response rate was 60.9%, 80.0%, 83.3% and 91.7% at weeks 4, 12, 24 and 48. [Conclusion] ABT was a possible treatment for biologic-naive patients with RA that had high disease activity and many complications.

## W57-1

### Early efficacy of denosumab, an anti-RANKL antibody, on osteoporosis in patients with rheumatoid arthritis from multicenter study

Yuji Hirano<sup>1</sup>, Yasuhide Kanayama<sup>2</sup>, Shuji Asai<sup>3</sup>, Shinya Hirabara<sup>1</sup>, Toshihisa Kojima<sup>3</sup>, Naoki Ishiguro<sup>3</sup>

<sup>1</sup>Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan, <sup>2</sup>Department of Orthopaedic Surgery and Rheumatology, Toyota Kosei Hospital, Toyota, Japan, <sup>3</sup>Department of Orthopaedic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

Conflict of interest: None

[Objectives] To investigate the early efficacy of denosumab (DMB) on osteoporosis in patients with rheumatoid arthritis (RA-OP) from multicenter study (TBCR-BONE). [Methods] 30 female cases with RA-OP were included in this study. BMD of lumbar spine (LS-BMD) and total hip (TH-BMD) and bone turnover markers (P1NP and TRACP-5b) were measured at baseline and 6month. [Results] Mean age was 70.6 yo. Mean RA duration was 14.0y. Mean DAS28-CRP was 2.33. 50% of cases had the past history of fracture. Mean FRAX was 26.3%. Daily teriparatide was used in 8 cases before DMB treatment. LS-BMD at 6m was significantly increased compared with baseline (5.5%). TH-BMD at 6m was significantly increased compared with baseline (3.5%). Mean decrease in P1NP and TRACP-5b were 46.5% and 45.25%, respectively. Change of BTMs was not significantly associated with change of BMD. There was no significant difference in change of BMD between PSL-concomitant group and no-PSL-concomitant group. There was also no significant differences in change of BMD between Biologics-concomitant group and no-Biologics-concomitant group. [Conclusion] DMB was effective in RA-OP. Change of BTMs was not significantly associated with change of BMD. DMB can be used and effective in various type of patients with RA-OP.

## W57-2

### Investigation of the efficacy and safety of Denosumab for the osteoporosis in collagen disease and rheumatoid arthritis patients

Keisuke Hagihara<sup>1</sup>, Yuki Kishida<sup>1</sup>, Miho Nakanishi<sup>1</sup>, Hideki Yoshikawa<sup>2</sup>  
<sup>1</sup>Department of Kampo Medicine, Osaka University Graduate School of Medicine, Osaka, Japan, <sup>2</sup>Department of Orthopedic Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

Conflict of interest: Yes

[Objectives] We investigated the efficacy and safety of Denosumab (Anti-RNKL antibody) for the osteoporosis in the collagen disease and RA patients. [Methods] We examined the 81 patients (RA24, SLE27, PMR6, Behcet's disease 6, DM4, MCTD3, others11, F:M=65:16, 55±14 years old, BMI 21.3±2.9) from 113 patients in treatment with Denosumab from July 2013. We evaluated the bone mass of the patients using DEXA, biochemical markers of bone metabolism and serum level of Ca before, 6 months and 1 year after treatment [Results] The clinical background of patients were as follows; the mean dosage of PSL5.4 ± 3.4mg (69/81), MTX7.1 ± 2.6mg (19/81), immunosuppressive agents (CYA6, FK506 5, MMF1, AZ1), biologics (ABT9, TCZ7, GLM3, ADA3, ETN1). BP drugs (MIN37, RIS 13, ALN4), PTH 4. Both BMD of L2-4 and Femur increased significantly (L2-4: 0.885±0.175→0.927±0.188→.952±0.216 (g/cm<sup>2</sup>), p<0.001 paired-t, Femur; 0.621±0.109→0.633±0.114→0.644±0.121 (g/cm<sup>2</sup>), p<0.001 paired-t). Urine level of NTx significantly decreased. The serum level of Ca slightly increased using active form of VitD. Hypocalcemia appeared after treatment in a RA patient with HD. [Conclusion] Denosumab is effective for the osteoporosis in RA and collagen patients. Further study is needed to determine the long-term safety of Denosumab.

### W57-3

#### Tocilizumab preserves hand and general bone mineral density in patients with active Rheumatoid Arthritis

Kou Katayama<sup>1</sup>, Satomi Abe<sup>2</sup>, Tamotsu Kamishima<sup>3</sup>

<sup>1</sup>Katayama Orthopedic Rheumatology Clinic, <sup>2</sup>Department of Orthopedic Surgery, Asahikawa Medical University, <sup>3</sup>Faculty of Health Science, Hokkaido University

Conflict of interest: None

[Objectives] To explore the effect of Tocilizumab (TCZ) on BMD of hand and general bone (the lumbar spine, femoral neck) in patients with RA. [Methods] A total of thirty-seven RA patients treated with TCZ were investigated. BMDs (g/cm<sup>2</sup>) of the lumbar spine (second to fourth vertebrae) and both femoral neck and hand were measured by dual-energy X ray absorptiometry (DEXA) using Prodigy. The BMD was measured before and 1 year after start of TCZ treatment. [Results] Baseline characteristic included: mean age 64.3 years old; sex male/female 5/32; mean disease duration 108 (3-408) months; previous TNF inhibitor use in 54.0%; methotrexate (MTX) use in 70.2%(mean 6.5mg/week); glucocorticoid use in 62.2%(mean 2.6 mg/day), bisphosphonate use in 38.0%; DAS28-ESR 5.78. Mean and medium of BMD of hand, lumbar spine, femoral neck from baseline to after 1 year were remained unchanged after 1 year of TCZ treatment. ΔBMDs in three parts were not affected by the existence of MTX, previous biologics except bisphosphonate for ΔBMD in lumbar spine. There were no significant correlation between ΔDAS28-ESR, ΔmTSS/year and the percent change of each BMD. [Conclusion] TCZ may preserve hand and general BMD regardless of ΔDAS28-ESR, ΔmTSS/year. Percent change of Lumbar BMD was affected by bisphosphonate.

### W57-4

#### The examination of the factors which affect the existence of low bone mass index in RA patients who has been taken the biological disease-modifying antirheumatic treatment

Kengo Takahashi<sup>1</sup>, Takao Setoguchi<sup>1,3</sup>, Katsuyuki Imamura<sup>2</sup>, Yoshiya Arishima<sup>2</sup>, Kenji Nakano<sup>2</sup>, Noriko Aoki<sup>2</sup>, Masaki Akimoto<sup>2</sup>, Hideo Ohtsubo<sup>2</sup>, Takemasa Matsuda<sup>2</sup>, Nobuhiko Sunahara<sup>2</sup>, Setsuro Komiyama<sup>1,3,4</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan, <sup>2</sup>Center of Rheumatism and Collagen Kagoshima Red Cross Hospital, <sup>3</sup>The Near-Future Locomotor Organ Medicine Creation Course (Kusunoki Kai), Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan, <sup>4</sup>Department of Medical Joint Materials, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan

Conflict of interest: None

[Objectives] Rheumatoid arthritis is a systemic inflammatory disease which can promote local joint deformity including erosions of bone. Os-

teoporosis promotes increased fracture risk. Several evidences showed that bDMARDs might be beneficial to bone metabolism and bone remodeling. We examined the bone mass index (BMI) of patients who has been taken bDMARDs treatment. [Methods]202 patients were examined BMI using femoral neck. 60 patients were YAM < 70 (osteoporosis group), 142 patients were YAM ≥ 70 (normal group). In addition, we examined the factors which affect the existence of low BMI in RA patients who has been taken bDMARDs treatment. The following variables were collected: age, gender, body mass index (BMI), disease duration, presence or absence of rheumatoid vasculitis or mutilans type of RA dose of methylprednisolone, CRP, DAS28-CRP, SDAI, CDAI, MHAQ, Steinbrocker criteria, presence or absence of vertebral and femoral neck fracture. [Reults] We examined the factors which affect the osteoporosis including age, gender, disease duration, and body mass index (BMI). The activities of Rheumatoid arthritis revealed no significant difference between osteoporosis group and normal group. [Conclusion] We should take care of rheumatism patients who have these factors of osteoporosis.

### W57-5

#### 1-year effect of treatment examination when we changed it from alendronate or risedronate to minodronate in osteoporosis treatment patients with rheumatoid arthritis

Takaaki Noguchi, Kosuke Ebina, Makoto Hirao, Kenrin Shi, Hideki Yoshikawa

Department of Orthopaedic Surgery, Graduate School of Medicine, Osaka University

Conflict of interest: Yes

[Objectives] It has been reported that BMD is increased by the switching from alendronate (ALN) / risedronate (RIS) to minodronate (MIN) in post-menopausal osteoporosis patients. The mechanism of osteoporosis in RA is showed by various factors and unlike that of post-menopausal osteoporosis, and the switching effect to MIN is unknown. [Methods] We performed 1-year prospective study in RA patients with osteoporosis switching from ALN / RIS to MIN (SG: n=80) and continuing ALN/RIS (CG: n=64). We examined BMD, bone markers (0, 6, 12months), new fracture rate and the factor associated with increasing of BMD in 1-year. [Results] After 1-year, BMD was increased by 3.9% in lumbar and 1.3% in proximal femur in SG, and increased by 1.2% in lumbar and decreased by 0.2% in proximal femur in CG. The change of TRACP-5b was 254.7→182.2→182.8mU/dl and P1NP was 30.5→25.3→24.0ng/ml in SG. New fracture rate was 7.8% in SG and 6.3% in CG. We performed multivariate analysis, so patients in aging, VitK non combination and decrease of bone marker of 6months are easy to increase BMD, and long-term of RA, VitK combination and PSL non combination change treatment of osteoporosis. [Conclusion] Switching ALN / RIS to MIN in 1-year seems effective when assessed by BMD increase in the treatment of RA osteoporosis.

### W57-6

#### The risk factors of bisphosphonate-related beaking (atypical femoral incomplete fracture) among patients with autoimmune diseases taking glucocorticoid; from a prospective longitudinal study for two years

Hiroe Sato<sup>1</sup>, Naoki Kondo<sup>2</sup>, Junichi Fujisawa<sup>2</sup>, Naoto Endo<sup>2</sup>, Chinatsu Takai<sup>1</sup>, Ayako Wakamatsu<sup>1</sup>, Yukiko Nozawa<sup>1</sup>, Takeshi Nakatsue<sup>1</sup>, Yoko Wada<sup>1</sup>, Takeshi Kuroda<sup>3</sup>, Masaaki Nakano<sup>4</sup>, Ichiei Narita<sup>1</sup>

<sup>1</sup>Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, <sup>2</sup>Division of Orthopedic Surgery, Niigata University Graduate School of Medical and Dental Sciences, <sup>3</sup>Health Administration Center, Niigata University, <sup>4</sup>School of Health Sciences, Faculty of Medicine, Niigata University

Conflict of interest: None

[Objectives] To identify the risk factors for bisphosphonate (BP)-related beaking (atypical femoral incomplete fracture) among patients with autoimmune diseases under glucocorticoid treatment. [Methods] One hundred and twenty five patients with autoimmune diseases taking BP were included and 116 patients underwent annual X-ray and serum bone metabolism markers for 2 years. The mean age was 54.5 years old (19-



84), 105 (90.5 %) were females, the mean disease duration was 13.2 years (1.2-43.9) and all of them were taking prednisolone (PSL); the mean dose was 10.0mg daily (0.5-25 mg). The mean duration of BP usage was 5.1 years (0.5-13.8). The X ray of femurs was examined and focal lateral cortical thickening was defined as beaking. [Results] Beaking was detected in 10 patients 15 lower extremities at the recruitment. In two year observation period, the frequency of beaking was increased to 12 patients 21 lower extremities. Patients with beaking showed longer BP treatment (6.1±1.0 years vs. 5.0±2.9 years,  $p=0.01$ ), higher ALP levels and lower urine NTX levels at the recruitment and higher ALP and BAP levels in two year observation period. [Conclusion] The regular screening for X-ray examinations of femurs is necessary to detect BP-related beaking.

### W58-1

#### There is a possibility that the patient he took eldelcalcitol for a long term will develop myalgia

Yusuke Kamba, Yoshihiro Mikawa

Japan Community Healthcare Organization, Tamatsukuri Hospital, Shimane, Japan

Conflict of interest: None

We experienced four cases where myalgia quickly disappeared after they stopped taking eldelcalcitol. The four cases were all of women. The average age was 74 (67-82) years. In three cases they took SERM and in a case BP at the same time. These four cases had six common aspects as follows: 1) The symptoms occurred gradually after they have taken eldelcalcitol more than six months. 2) They had pains in their various proximal muscles such as lumbar and femoral. 3) No abnormal musculoskeletal and neurological findings which caused pains were recognized in the imaging study. 4) CRP, ESR and serum calcium were all normal. 5) None of Analgesic drugs like NSAIDs, steroid, or pregabalin had effect on their symptoms. 6) Their symptoms disappeared quickly within three days after they stopped taking eldelcalcitol. And in three cases there was no recurrence of the myalgia after eldelcalcitol was changed to alfacalcidol. We guessed the cause of this myalgia from the common aspects of these four cases. Because the half life of eldelcalcitol is longer than that of other vitamin D preparations, eldelcalcitol tends to accumulate in the body when used for a long term. As a result, the proximal muscular strength reinforcement effect which vitamin D has intrinsically occurred excessively, accordingly this myalgia appeared.

### W58-2

#### Relationship between low serum 25 (OH) D concentration and bone mass or bone turnover markers in patients with rheumatoid arthritis. -TOMORROW research -

Naoki Takada<sup>1</sup>, Kentaro Inui<sup>1</sup>, Tatsuya Koike<sup>2,3</sup>, Masahiro Tada<sup>1</sup>, Yuko Sugioka<sup>1,2</sup>, Kenji Mamoto<sup>1</sup>, Tadashi Okano<sup>1</sup>, Hiroaki Nakamura<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery Osaka City University Graduate School of Medicine, <sup>2</sup>Rheumatology Center for Senile Degenerative Disorders Osaka City University Graduate School of Medicine, <sup>3</sup>Shirahama Hamayu Hospital Welfare Foundation Search Institute for Bone and Arthritis Disease

Conflict of interest: None

[Objectives] It is known that serum 25 (OH) D concentration (VD) is lower in the patients with rheumatoid arthritis (RA), however, there is a lack of reports of the relationship between VD and bone mass or metabolism markers. We are conducting the prospective cohort study (TOMORROW study: UMIN000003876) for RA patients and age-, sex-matched healthy volunteers (Vo) from 2010. In this study, we compared bone density, bone metabolic markers of RA patients with those of Vo. [Methods] The characteristic, bone metabolic markers (urinary pentosidine, homocysteine, NTX and osteocalcin), and lower limb bone density of the study population were measured. [Results] Four hundred thirteen (208 RA patients, 205 Vo) were enrolled. Mean age was 58 years. In RA patients, bone density was significantly lower ( $p<0.01$ : t-test), urinary NTX, pentosidine, and homocysteine were higher ( $p<0.01$ ,  $p<0.01$ ,  $p<0.05$ , respectively) than those of Vo. VD in RA was lower ( $p<0.01$ ). Multiple linear regression analysis revealed there was no significant relationship between

VD and bone density or pentosidine. [Conclusion] Low bone mass and low bone quality found in RA patients was not related with low VD.

### W58-3

#### The dosage of glucocorticoid is a risk factor for falls in rheumatoid arthritis patients—the 4th year results of the TOMORROW study-

Yuko Sugioka<sup>1</sup>, Tatsuya Koike<sup>1,2</sup>, Kenji Mamoto<sup>3</sup>, Tadashi Okano<sup>3</sup>, Masahiro Tada<sup>3</sup>, Kentaro Inui<sup>4</sup>, Hiroaki Nakamura<sup>3</sup>

<sup>1</sup>Center for Senile Degenerative Disorders (CSDD), Osaka City University Medical School, Osaka, Japan, <sup>2</sup>Search Institute for Bone and Arthritis Disease (SINBAD), Shirahama Foundation for Health and Welfare, <sup>3</sup>Orthopaedic Surgery, Osaka City University Medical School, Osaka, Japan, <sup>4</sup>Rheumatology, Osaka City University Medical School, Osaka, Japan

Conflict of interest: None

[Objectives] Patients with rheumatoid arthritis (RA) might be at increased risk of falling. The present study prospectively determines the incidence of falls and their risk factors in patients with RA who participated in the TOMORROW study that was started in 2010. [Methods] We evaluated the occurrence of falls for a period of 4 years in 208 RA (58 years) and 205 age- and sex-matched volunteers (Vo: 57 years). [Results] There is no difference in incidence of falls between RA (47.5%) and Vo (40.6%) during 4 years. The patients with RA fell significantly more often than Vo (2.9 vs. 2.0 falls/4y;  $p = 0.02$ ). After adjusting for risk factors, multiple regression analysis identified that a history of falls was the most significant parameter associated with the incidence of falls (odds ratio: 2.99,  $p<0.001$ ) in all participants. Total amount of GC during 4 years and anti-CCP antibody at the entry appeared to be related with the number of falls after adjusting for fall risk factors (GC:  $\beta=0.156$ ,  $p=0.028$ , CCP:  $\beta=0.275$ ,  $P<0.001$ ) in RA. [Conclusion] There is no difference in incidence of falls between RA and Vo during 4 years. However, multiple fallers in RA patients were higher than that in Vo. RA patients with high doses of GC and high titer of anti-CCP antibody tend to fall more frequently.

### W58-4

#### Analysis of bone in TCTA transgenic or knockout mice: a preliminary study

Shigeru Kotake, Yuki Nanke, Toru Yago, Manabu Kawamoto, Tsuyoshi Kobashigawa, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: None

[Objectives] We have demonstrated that T-cell leukemia translocation-associated gene (TCTA) play an important role in human osteoclastogenesis (Kotake et al. Bone 2009). In the current study, we explored 2 hypothesis. A: In TCTA transgenic (Tg) mice, osteoclastogenesis increases and bone volume decreases. B: In TCTA knockout (KO) mice, osteoclastogenesis decreases and bone volume increases. [Methods] TCTA-Tg mice were constructed in 2 types: general expression type (TCTA-Tg1) and osteoclast (Oc)-specific expression type (TCTA-Tg2). TCTA-KO (Oc specific) mice were also constructed. Bone analysis was performed compared with wild type (WT) mice. [Results] In TCTA-Tg mice, bone volume decreased with increased both osteoclastogenesis and bone formation, supporting hypothesis A. In TCTA-KO mice, osteoclastogenesis decreased, supporting hypothesis B; however, bone volume decreased with decreased bone formation. [Conclusions] In TCTA Tg mice, bone volume decreased. On the other hand, in TCTA-KO mice, osteoclastogenesis decreased.

### W58-5

#### Siglec-15 mediates periarticular bone loss but not joint destruction in murine antigen-induced arthritis

Tomohiro Shimizu, Norimasa Iwasaki

Department of Orthopaedic Surgery Hokkaido University Graduate School of Medicine

Conflict of interest: None

Multiple immunoreceptors, which associate with ITAM adaptor pro-

teins including DAP12 and FcR have been identified in osteoclast lineage cells, and some of them are shown to be involved in arthritis induced bone destruction. Siglec-15 is an immunoreceptor that regulates osteoclast development and bone resorption in association with DAP12; however, it remains unknown whether Siglec-15 is involved in arthritis induced bone lesions. In this study, we examined the role of Siglec-15 in the development of bone lesions induced by joint inflammation using a murine AIAModel. The degree of joint inflammation, cartilage and subchondral bone destruction in *KO* mice were comparable to that in WT mice, indicating that Siglec-15 is not involved in the development of arthritis and concomitant cartilage and subchondral bone destruction. On the other hand, the degree of periarticular bone loss seen in the proximal tibia of arthritis knee was significantly less in *KO* mice compared to WT mice. Our data suggest that Siglec-15 is a therapeutic target for periarticular bone loss but not for joint destruction in inflammatory arthritis such as rheumatoid arthritis.

## W59-1

### Reactivation of hepatitis B virus in patients with rheumatoid arthritis treated with biologic agents

Yumiko Inoue, Yuko Kaneko, Hironari Hanaoka, Hidekata Yasuoka, Katsuya Suzuki, Tsutomu Takeuchi  
Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine

Conflict of interest: None

[Objectives] To investigate the prevalence of hepatitis B virus (HBV) infection in patients with rheumatoid arthritis (RA) and to assess the safety of biologics. [Methods] 538 outpatients with RA who commenced biologic agents treatment since 2012 until 2014 in Keio University Hospital were retrospectively reviewed. All patients were examined for HBsAg, HBsAb and HBeAb before the treatment, then patients who were positive for any marker were monitored for HBV-DNA regularly. [Results] Of the 538 patients, three patients (0.6%) were positive for HBsAg, 68 patients (12.4%) were positive for HBsAb, 56 (10.4%) patients were positive for HBeAb. In the three patients with HBsAg positive, HBV-DNAs were 2.1, 3.4, 3.5 Log copy/ml, respectively, and they started Entecavir before initiating biologic agents. On the other hand, HBV-DNA was not detected in any patient with HBsAb and/or HBeAb positive that were regarded as having prior infection. During the follow-up period, HBV-DNA was never detected in any patient. [Conclusion] Among the prior infection group and the carrier group treated with concomitant Entecavir, there was no reactivation of hepatitis B virus during the treatment of biologic agents.

## W59-2

### Different modality in suppression of pituitary and adrenal functions by glucocorticoid therapy in patients with rheumatic diseases

Natsuki Fujio, Shotaro Masuoka, Mai Kawazoe, Emiko Shindo, Hiroshi Sato, Kotaro Shikano, Makoto Kaburaki, Sei Muraoka, Nahoko Tanaka, Kaichi Kaneko, Tatsuhiro Yamamoto, Natsuko Kusunoki, Tomoko Hasunuma, Shinichi Kawai  
Division of Rheumatology, Department of Internal Medicine, School of Medicine, Toho University

Conflict of interest: None

[Objectives] Suppression of pituitary-adrenal (PA) function by glucocorticoid (GC) therapy is well-known, however, detailed investigation has not been studied yet. We then used CRH stimulation test, to examine the process of suppression of PA function by GC therapy in patients with rheumatic diseases (RD). [Methods] Thirty-nine patients with RD (66.4±15.4 y.o, M±SD) who received initial GC therapy were prospectively enrolled. The CRH stimulation test was performed at 0, 2, and 4 wk after starting GC therapy. Patients were divided into two groups with prednisolone daily dose of 30 mg or more (high-dose group; HD), and equal or less than 15 mg (low-dose group; LD). The basal concentrations of ACTH and cortisol (F) in blood, and their increased values ( $\Delta$ ACTH and  $\Delta$ F) after CRH stimulation were examined. [Results] Basal and  $\Delta$  of ACTH and F were significantly reduced after GC therapy in HD. In LD,  $\Delta$ ACTH was not suppressed after GC therapy. In contrast, basal and  $\Delta$ F were significantly reduced. [Conclusion] PA functions were sup-

pressed in HD. In LD, the pituitary function was not suppressed by GC therapy, however, the adrenal function was remarkably suppressed. It is suggested that adrenal suppression by GC therapy might be caused not only by feedback regulation via pituitary suppression.

## W59-3

### Sarcopenia and Rheumatoid Arthritis in the Kurama Cohort

Mie Torii<sup>1</sup>, Motomu Hashimoto<sup>2</sup>, Akiko Hanai<sup>3</sup>, Takao Fujii<sup>2</sup>, Masahiro Ishikawa<sup>2</sup>, Moritoshi Furu<sup>2</sup>, Hiromu Ito<sup>2,4</sup>, Masahide Hamaguchi<sup>5</sup>, Chikashi Terao<sup>6</sup>, Wataru Yamamoto<sup>2,7</sup>, Miyabi Uda<sup>3</sup>, Kazuko Nin<sup>3</sup>, Hidenori Arai<sup>3</sup>, Tsuneyo Mimori<sup>2,8</sup>

<sup>1</sup>Center for the Promotion of Interdisciplinary Education and Research, Kyoto University, Kyoto, Japan, <sup>2</sup>Department of the Control for Rheumatic Diseases Graduate School of Medicine, Kyoto University, Kyoto, Japan, <sup>3</sup>Department of Human Health Graduate School of Medicine, Kyoto University, Kyoto, Japan, <sup>4</sup>Department of Orthopaedic Surgery Graduate School of Medicine, Kyoto University, Kyoto, Japan, <sup>5</sup>Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine Eraduate School of Medical, Kyoto, Japan, <sup>6</sup>Unit of Human Disease Genomics Center for Genomic Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan, <sup>7</sup>Department of Health Information Management, Kurashiki Sweet Hospital, Okayama, Japan, <sup>8</sup>Department of Rheumatology and Clinical Immunology Graduate School of Medicine, Kyoto University, Kyoto, Japan

Conflict of interest: None

[Objectives] Sarcopenia is characterized by loss of muscle strength and muscle mass, leading to falls and health disorder. Patients with RA may have a high risk for sarcopenia due to inflammation and steroid use. The purpose of the study was to determine the prevalence of sarcopenia in RA patients and to elucidate the contributing factors that affect the development of sarcopenia. [Methods] We measured muscle strength, muscle mass, and walking speed in 342 RA patients for the diagnosis of sarcopenia. We also determined the RA activity, bone mineral density, and medications of each patient. [Results] 48.5% of RA patients had sarcopenia. Additionally, RA patients with sarcopenia showed a higher incidence of falls and fracture along with lower bone mineral density than non-sarcopenic RA patients. The use of biologics had a negative effect of the development of sarcopenia, while RA activities, and steroid use were positively associated with that of sarcopenia by multivariate logistic regression analysis. [Conclusion] Our study indicates that sarcopenia is associated with falls and fractures along with osteoporosis in RA patients. Additionally, higher RA activities and steroid use are risk for sarcopenia and biologics use might lead to amelioration of muscle loss.

## W59-4

### Clinical characteristics of the in-patients who fell down during hospitalization to our division

Ayako Kokuzawa, Masahiro Iwamoto, Takao Nagashima, Katsuya Nagatani, Yasuyuki Kamata, Yoichiro Akiyama, Kyoko Honne, Akihito Maruyama, Takamasa Murosaki, Koichi Takeda, Jun Nakamura, Seiji Minota  
Division of Rheumatology and Clinical Immunology, Jichi Medical University, Tochigi, Japan

Conflict of interest: None

[Objectives] To search for features of the hospitalized patients with rheumatic disease who fell down. [Methods] We extracted the clinical data of the patients who fell down during hospitalization from 2009 through 2013 and compared them with those who did not. The extracted items were gender, age, disease, dosage of corticosteroids, and length of hospital stay. [Results] Of 1918 patients who were hospitalized, 77 (4.0%) experienced falls and total number of falls was 87. Twenty-seven men (35.1%) and 50 women (64.9%) fell down at least once during hospitalization and the median age was 69; the median dosage of corticosteroids was 20 mg/day and the median length of hospital stay was 36 days. Five hundred and seven men (27.5%) and 1334 women (72.5%) had never fallen down during hospitalization and the median age was 62; the median dosage of corticosteroids was 9 mg/day and length of hospital stay was 14 days. [Conclusion] Older age, higher dosage of corticosteroids,

and longer hospital stay were risk factors of falling down in in-patients with rheumatic disease. We also need to pay attention to patients with muscle weakness and neuropathy resulting from rheumatic diseases.

### W59-5

#### Examination about usefulness of ultrasound in polymyalgia rheumatica

Asuka Inoue<sup>1</sup>, Yuji Nozaki<sup>1</sup>, Tetsu Itami<sup>1</sup>, Kenji Sakai<sup>1</sup>, Chiemi Tasaki<sup>1</sup>, Shinkai Ri<sup>1</sup>, Taeko Yumoto<sup>2</sup>, Kayo Asato<sup>1</sup>, Toshihiko Shiga<sup>1</sup>, Shoichi Hino<sup>1</sup>, Tomohiro Yano<sup>1</sup>, Kazuya Kishimoto<sup>1</sup>, Yasuaki Nagare<sup>1</sup>, Hideki Shimazua<sup>2</sup>, Koji Kinoshita<sup>2</sup>, Masanori Funauchi<sup>1</sup>, Itaru Matsumura<sup>1</sup>

<sup>1</sup>Kindai University School of Medicine, Osaka, Japan, <sup>2</sup>Kindai University Sakai Hospital, Osaka, Japan

Conflict of interest: None

[Objective] Clinical symptoms, laboratory findings and ultrasonographic (US) findings in the course of the treatment were compared in the patient with polymyalgia rheumatica (PMR). [Method] Twenty-eight patients who fulfilled ACR/EULAR criteria of PMR (9 male, 19 female, mean age 75.5 y.o. [64 to 88]), diagnosed from October 2011 to October 2014, were included. Initial dose of prednisolone was 15 mg/day, and no immunosuppressants were used. Clinical symptoms (VAS, morning stiffness, HAQ), laboratory findings (MMP-3, CRP, ESR) and US were evaluated and compared at the baseline and 24, 54 weeks after the beginning of the treatment. By US, bilateral shoulder long head biceps (LHB), especially the synovial thickness of them was observed. [Result] A significant improvement in the clinical symptoms and laboratory findings was observed at 24 week ( $P<0.01$ ), and a significant decrease in the synovial thickness of LHB was also found at 24 week ( $P<0.01$ ). Improvement of these parameters were maintained at 54 weeks of the treatment. [Conclusion] We suggest that US might be a useful tool in addition to the clinical symptoms and laboratory findings for more precise assessment of the response to the treatment in PMR.

### W59-6

#### Considering Autoinflammatory Diseases in General Internal Medicine: Analysis of 44 Patients with Fever of Unknown Origin

Junko Maeda, Junwa Kunimatsu

Department of General Internal Medicine, National Center for Global Health and Medicine Hospital

Conflict of interest: None

[Objective] The etiological spectrum of FUO is wide. It is a diagnostic challenge for general internists, as well as rheumatologists. Our aims are to elucidate the underlying diseases as a cause of FUO in our department and to discuss the difficulty of adapting a patient with recurrent fevers to FUO criteria. [Methods] We reviewed all medical records of patients who visited our department from 2012 through 2014. Patients were selected by following criteria: they had fever  $>38.0^{\circ}\text{C}$  on the first visit; or they had fever as a chief complaint. [Results] A total 976 patients were included. 44 patients met the criteria for classic FUO, and 8 of them diagnosed as FMF. [Discussion] This study showed the real trends of causal disease in our department. It is noteworthy that our series had 18% of FMF patients. The main reason is that we fully recognize this disease regardless of rarity. Indeed, we consider that many patients potentially remain underdiagnosed for several reasons. First, the duration of fever is too short to be recognized. Second, inflammation-free intervals are seen. Lastly, FMF attack is not always accompanied by fever. "Illness of more than 3 weeks' duration" does not mean only a continuous fever. [Conclusion] We should recognize recurrent fevers as a chronic episodic FUO.

### W60-1

#### Clinical analysis of 30 rheumatoid arthritis patients complicated by malignant lymphoma, especially methotrexate-related lymphoproliferative disorder

Takuma Wada, Akinori Kunibu, Maiko Yanagisawa, Takashi Maruyama, Daisuke Ikuma, Hideyuki Tachibana, Yuki Shimada, Yasufumi Shindo, Yoshihiro Yoshida, Kazuhiro Yokota, Yasuto Araki, Hiroshi Kajiyama, Haruhiko Akiba, Kojiro Sato, Yuji Akiyama, Toshihide Mimura

Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Saitama, Japan

Conflict of interest: None

[Objectives] It is known that methotrexate (MTX) or rheumatoid arthritis (RA) itself induce lymphoproliferative disorder (LPD), especially malignant lymphoma (ML). To evaluate clinical features of these conditions precisely, RA patients (pts) complicated by ML in our hospital were analyzed. [Methods] We analyzed clinical characteristics and courses of 30 RA pts complicated by ML retrospectively and compared them with 24 non-ML RA pts. [Results] Thirty pts (23 female), mean;  $62.5\pm 10.0$  years, disease duration of RA;  $9.2\pm 0.6$  years included 21 MTX-LPD pts. The dose of MTX was under 8mg/week in 13 among 15 pts and duration of MTX administration was under 5 years in 11 among 15 pts. The histological type of MTX-LPD was diffuse large B-cell lymphoma in 16 pts. Four pts were died. The levels of CRP were elevated 2 months before ML onset and those of LDH were elevated at the time ML was diagnosed. The levels of lymphocytes, Hb and PLT were low, and those of LDH, CRP and ESR were high, compared with those in non-ML pts. [Conclusions] We clarified clinical characteristics of RA pts complicated with ML. MTX-LPD developed in many pts in spite of low dose MTX and relapsed pts existed after spontaneous regression of ML due to MTX cessation. The levels of CRP might be elevated before diagnosis of ML.

### W60-2

#### Examination of 19 cases that developed a lymphoproliferative disease (LPD) during methotrexate (MTX) treatment, improved by discontinuation or decrease of dosage

Noriyuki Hayashi, Hitoshi Goto, Kae Hamamoto, Maki Yoda, Koichiro Yoda, Shinsuke Yamada, Masaaki Inaba

Rheumatology, Osaka City University Hospital

Conflict of interest: None

[Objectives] We examined the clinical features of the improved cases by discontinuation or decrease of dosage of MTX in the MTX-LPD. [Methods] We retrospectively examined a patient background, a clinical presentation, a histopathology, and clinical course in 19 patients from 2006 through 2014. [Results] These cases were average age 64.5 y.o. (37-81), 3 male, 16 female, 8.1 mg/week of MTX average dosage, 1,510 mg (312-6110 mg) of MTX average total doses, and mean DAS28 (CRP) 3.65 (2.3-5.46) at the MTX-LPD onset. Lymph node biopsy performed in 16 patients showed reactive lymphadenopathy syndrome 6, Diffuse large B-cell lymphoma (DLBCL) 5, Hodgkin's lymphoma 3, non-specific Peripheral T-cell lymphoma 1, primary effusion lymphoma (PEL) 1. Blood EBV-DNA showed 2 positive, 2 negative cases in 4 cases. 13 of 16 cases that discontinued MTX improved spontaneously, but 3 cases were given chemotherapy that showed curative effect. 3 cases that reduced without discontinuation of MTX were spontaneously improved. [Conclusion] Most of MTX-LPD spontaneously improved by MTX discontinuation. The risk of development of MTX-LPD was not clear. There was no difference in the ratio of the histopathology and prognostic association compared with malignant lymphoma. MTX-LPD requires follow-up for a certain period.

### W60-3

#### Clinicopathological analysis of 8 cases of rheumatoid arthritis accompanying lymphoproliferative disorders under treatment of methotrexate

Hiroshi Fujii, Shigeto Horita, Yuhei Fujisawa, Takeshi Zoshima, Hiromi Nuka, Satoshi Hara, Yasunori Suzuki, Kiyoaki Ito, Motohiko Aizu, Kazunori Yamada, Mitsuhiro Kawano

Division of Rheumatology, Department of Internal Medicine, Kanazawa University Hospital

Conflict of interest: None

[Purpose and Methods] Management of rheumatoid arthritis (RA) with methotrexate related lymphoproliferative disorders (MTX-LPD) is challenging. Courses of 8 cases of LPD with RA were retrospectively analyzed to characterize RA with MTX-LPD. [Result] 2 males and 6 fe-

males were evaluated. MTX was administered for 5.8 years on average. Median cumulative dose was 259 mg. EBV-DNA load was more than 2000 copies/ml in 4, and less than 500 copies/ml in 2 cases. EBER-ISH was positive in 6 and negative in 2 cases. After the diagnosis of LPD, MTX was withdrawn in all cases. 2 cases underwent R-CHOP and 1 case received Rituximab (RIT) alone. LPD of 3 cases were surgically removed. 2 cases did not receive any treatment. All LPD regressed and no relapse was observed for 12.9 months after withdrawal of MTX. Median DAS28-CRP was 2.67 at the diagnosis of LPD. 12.9 months after discontinuation of MTX, DAS28-CRP became 2.69. During this period, RA was treated with low dose prednisolone in 5, RIT in 2, tacrolimus in 2, iguratimod in 1, and bucillamin in 1 case. Despite of these treatments, 3 cases experienced flare up of RA. [Conclusion] Treatment with RIT was not effective enough without MTX in one case. More cases are needed to draw strategies to treat RA with MTX-LPD.

#### **W60-4**

##### **Study of five rheumatoid arthritis patient complicated with methotrexate lymphomas**

Shinichiro Nishimi, Airi Nishimi, Yoko Miura, Ryo Yanai, Ryo Takahashi, Kuninobu Wakabayashi, Takeo Isozaki, Nobuyuki Yajima, Yusuke Miwa, Tsuyoshi Kasama

Division of Rheumatology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

Conflict of interest: None

**Objective;** Five rheumatoid arthritis (RA) patients complicated with methotrexate (MTX) lymphomas (ML) were examined about patient background, clinical feature and pathological histology. **Method;** We studied patient background, clinical feature and pathological histology about 5 RA patients who were visited in our division. **Result;** Mean age was 70.2 yrs old, mean time to ML diagnosis from the RA onset was 6.8 year, the mean dose period of MTX was 3.8 years and average dose of MTX was 7.2mg/w. Fever, anorexia, dyspnea, cervical lymphadenopathy and tonsil tumor were found for a clinical feature about onset of ML. The nodal lesion was found a lot in a neck, supraclavicular fossa, a mediastinum, a paraaortic lymph node, spleen, and the extra nodal disease was found in 2 (lung). As for the histologic type, diffuse large B-cell lymphoma (DLBCL) was 3, Hodgkin's lymphoma (HL) was one and one was unknown. All of 4 cases which examined EBER in on pathological testing were positive. All cases of DLBCL were stopped MTX and improving; 1 case of HL was treated by chemotherapy. **Conclusions;** In our division, clinical characteristic of MTX lymphoma were older age, the histologic type is much DLBCL, and mean time to ML diagnosis from the RA onset is short, and few MTX dose and a little extra nodal disease.

#### **W60-5**

##### **Usage survey on biologic DMARDs for patients with rheumatoid arthritis complicated with a malignant tumor**

Takahiro Seno<sup>1,2</sup>, Risa Sagawa<sup>2</sup>, Aiko Tominaga<sup>2</sup>, Takashi Kida<sup>2</sup>, Amane Nakabayashi<sup>2</sup>, Ken Murakami<sup>2</sup>, Aihiro Yamamoto<sup>2</sup>, Ryo Oda<sup>3</sup>, Toshikazu Kubo<sup>1,3</sup>, Masataka Kohno<sup>2</sup>, Yutaka Kawahito<sup>2</sup>

<sup>1</sup>Department of Rheumatic Diseases and Joint Function, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>2</sup>Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>3</sup>Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: Yes

**[Objectives]** We show the usage of biologic DMARDs for patients with rheumatoid arthritis (RA) complicated with a malignant tumor. **[Methods]** We extract patients with RA who were complicated with malignant tumor or who have history of malignancy from our outpatient database. And we research some parameters; disease name, biologic DMARDs, non-biologic DMARDs, disease activity. **[Results]** We analyzed 18 RA patients with malignancy. 14 patients were solid tumors and 4 were blood tumors. 5 patients were within 5 years after remission for solid tumors, and 4 were in blood tumors. Etanercept (ETN), tocilizumab (TCZ) and abatacept (ABT) were mainly used for these conditions. In

non-biologic DMARDs, about 50% patients were prescribed MTX, and the patients were passed more than 5 years by remission. In contrast, no MTX was used for blood tumor patients. **[Conclusion]** It was different in the usage of biological and non-biological DMARDs from solid tumors and blood tumors. ETN, TCZ, ABT were predominantly prescribed.

#### **W60-6**

##### **The evaluation of presepsin in rheumatic disease patients**

Noriaki Yo, Takashi Yamane, Chihiro Tanaka  
Kakogawa West City Hospital, Hyogo, Japan

Conflict of interest: None

**[Introduction]** Presepsin (CD14-st; soluble CD14-subtype) is present in macrophages, monocytes, granulocytes and their cell membranes, and produced by circulating plasma proteases activating cleavage of soluble CD14 (sCD14). We measured presepsin for screening test of sepsis. **[Object]** evaluate presepsin in rheumatic disease patient diagnosed as acute infection **[Methods]** A cohort study was performed in our hospital from April 2014 to October 2014. Total 28 rheumatic disease patients with fever diagnosed as acute infection were enrolled. Plasma presepsin, C-reactive protein levels, white blood cell counts were measured and investigated their immunosuppressants' dose. Presepsin was measured by chemiluminescent immunoassay (Pathfast; LSI medicine co.) **[Results]** 28 patients were enrolled. 22 patients were diagnosed as bacterial infection and their average presepsin level is 338.1±302.9pg/ml, 6 patients were diagnosed as non-bacterial infection and their average presepsin level is 309.1±322.4pg/m. There is no statistical significant different. **[Conclusion]** Presepsin level is lower in high dose immunosuppressant user, and there is no statistical significant different between bacterial infection and non-bacterial infection. We will investigate about presepsin cutoff level and accumulate this study.

#### **W61-1**

##### **Role of innate immunity in the development of corticosteroid-induced osteonecrosis of the femoral head**

Shunichiro Okazaki<sup>1,2</sup>, Satoshi Nagoya<sup>1</sup>, Motohisa Yamamoto<sup>4</sup>, Chisako Suzuki<sup>4</sup>, Yui Shimizu<sup>4</sup>, Hiroki Takahashi<sup>4</sup>, Hiromasa Inoue<sup>2</sup>

<sup>1</sup>Dept. of Musculoskeletal Biomechanics & Surgical Dev., Sapporo Medical University, Japan, <sup>2</sup>Dept. of Legal Med., Sapporo Medical University, Japan, <sup>3</sup>Dept. of Orthopedic Surgery, Sapporo Medical University, Japan, <sup>4</sup>Dept. of Gastroenterology, Rheumatology and Clinical Immunology, Sapporo Medical University, Japan

Conflict of interest: Yes

**[Objectives]** TLR has been reported to play any role in autoimmunity. We previously reported that 3 times of corticosteroid treatment after 2 times of injection of lipopolysaccharide, a ligand of TLR4, induces osteonecrosis of the femoral head (ONFH) in rats. Therefore, it is suggested that innate immune signaling via TLR plays a role of the pathogenesis of corticosteroid-induced ONFH. Therefore, we hypothesized that administration of these ligands for TLR4 or TLR7 or TLR9 and after that the treatment with methylprednisolone (MPSL) induces ONFH in rats. **[Methods]** Male wistar rats were randomly divided into four groups. Each group rats were given saline or ligand of TLR4 or TLR7 or TLR9 on Day 1 and methylprednisolone on Day 2. Histopathological analyses were performed. **[Results]** ONFH was observed in almost 50% of rats in groups given ligand of TLR and MPSL. By contrast, no ONF was observed in the saline with MPSL group. **[Conclusion]** In the present study, we show that TLRs ligand is required for ONFH to develop. It was reported that TLRs signaling contribute to pathogenesis of underlying diseases such as SLE. Present study confirmed that ONFH did not develop after steroid treatment alone. Therefore, innate immune signaling via TLR contributes pathogenesis of corticosteroid-induced ONFH.

#### **W61-2**

##### **Effect of transcription factor activity in the development of corticosteroid-induced osteonecrosis of the femoral head**

Shunichiro Okazaki<sup>1</sup>, Satoshi Nagoya<sup>1</sup>, Motohisa Yamamoto<sup>4</sup>, Chisako Suzuki<sup>4</sup>, Yui Shimizu<sup>4</sup>, Hiroki Takahashi<sup>4</sup>, Hiromasa Inoue<sup>2</sup>

<sup>1</sup>Dept. of Musculoskeletal Biomechanics & Surgical Dev., Sapporo Medical University, Japan, <sup>2</sup>Dept. of Legal Med., Sapporo Medical University, Japan, <sup>3</sup>Dept. of Orthopedic Surgery, Sapporo Medical University, Japan, <sup>4</sup>Dept. of Gastroenterology, Rheumatology, and Clinical Immunology, Sapporo Medical University, Japan

Conflict of interest: Yes

[Objectives] We previously reported that TLR signaling contribute to the development of ONFH. The reason for corticosteroid therapy for inflammatory diseases is related to their anti-inflammatory and immunosuppressive activities. Thus, we hypothesized that the effect of corticosteroid for transcription factors may contribute to the pathogenesis of ONFH. [Methods] Male Wistar rats were randomly divided into three groups. Each group rats were given ligand of TLR7 on Day 1 and Saline or methylprednisolone with or without BAY11-7082. NF- $\kappa$ B and IRF7 activity were assessed. [Results] The activity of NF- $\kappa$ B was repressed significantly in rats treated with MPSL at 1 day. However, MPSL treatment did not alter IRF7 activity. Co-administration of BAY11-7082 with MPSL was found to interfere with the development ONFH. The activity of IRF7 decreased significantly at 1 day in rats administered BAY11-7082. [Conclusion] Our results suggest that ONFH results from the activation NF- $\kappa$ B and IRF7, followed by a subsequent reduction in NF- $\kappa$ B activity by corticosteroid treatment, whereas IRF7 activity is not affected by corticosteroid treatment. In the present study, co-administration of BAY11-7082 and MPSL significantly lowered the incidence of ONFH through a repression in IRF7 activity

### W61-3

#### Diagnosis of AA amyloidosis by detection of AA76 on the abdominal fat materials

Toshiyuki Yamada<sup>1</sup>, Yasuaki Okuda<sup>2</sup>, Takeshi Kuroda<sup>3</sup>  
<sup>1</sup>Department of Clinical Laboratory Medicine, Jichi Medical University, <sup>2</sup>Centre of Rheumatology, Dohgo Spa Hospital, <sup>3</sup>Niigata University Health Administration Center

Conflict of interest: None

[Objectives] AA amyloidosis is diagnosed by histological examination on the gastric biopsy samples. Although abdominal fat is easy to assess, it is often difficult to judge Congo red results. AA76, amino-terminal end by degradation of precursor SAA, is almost always present in AA amyloid deposits. We have shown that positive ratio of AA76 is higher than that of histology in gastric specimens from AA amyloidosis patients. Here, the strategy was applied to abdominal fat samples. [Methods] Abdominal fat was aspirated from 8 patients, who were already diagnosed AA amyloidosis, and one patinet, who was finally denied. The samples were subjected to SDS-PAGE followed by immunoblotting with anti-SAA. The AA76 band was in agreement with the electrophoretic mobility of recombinant AA76. [Results] All 8 amyloid patients were positive for AA76 whlle non amyloid one was negative. [Conclusion] This method is so highly sensitive that not much volume of sample is required. We propose that this method is to be used prior to biopsy on gastrointestinal tract or kidney.

### W61-4

#### Analysis of AA amyloid formation using human PBMC cultures – part 2 –

Wataru Ishii<sup>1</sup>, Kenichi Ueno<sup>1</sup>, Dai Kishida<sup>1</sup>, Yasuhiro Shimojima<sup>1</sup>, Shuichi Ikeda<sup>1</sup>, Toshiyuki Yamada<sup>2</sup>, Juris Liepnieks<sup>3</sup>, Barbara Kluge-Beckerman<sup>3</sup>, Merrill D. Benson<sup>3</sup>

<sup>1</sup>Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, <sup>2</sup>Department of Clinical Laboratory Medicine, Jichi Medical University, <sup>3</sup>Department of Pathology and Laboratory Medicine, Indiana University School of Medicine

Conflict of interest: None

[Objectives] We have recently achieved human serum amyloid A (SAA)-derived amyloid formation in cultures of human peripheral blood mononuclear cells (PBMC) using serum-free medium. In this study, we analyzed AA amyloid formation using human PBMC cultures. [Methods]

PBMC were cultured in medium supplemented with recombinant SAA to make AA amyloid. AA amyloid and SAA fragments in medium were characterized by immunoblotting. CCL2 levels in medium were measured by ELISA. [Results] The disappearance of SAA from medium occurred faster in serum-free medium than medium with fetal calf serum. Medium collected from cells after the first 2 days of incubation with SAA contained significantly more CCL2 than medium from control cultures without SAA. Some protease inhibitors changed the composition of AA amyloid and SAA fragments in medium, but they did not inhibit amyloid formation. [Conclusion] Our results suggest that some serum components inhibit AA amyloid formation. And monocyte activation by CCL2 is important for AA amyloid formation.

### W61-5

#### Treatment of biologics for amyloid A amyloidosis secondary to rheumatoid arthritis

Tadashi Nakamura<sup>1</sup>, Hirokazu Takaoka<sup>1</sup>, Yuko Watanabe<sup>1</sup>, Kiyoshi Migita<sup>2</sup>

<sup>1</sup>Kumamoto Shinto General Hospital, <sup>2</sup>Nagasaki Medical Center

Conflict of interest: None

The principal aim in treating RA patients with AA amyloidosis is to switch off SAA production, by controlling the RA inflammatory process. Etanercept (ETN) can reduce serum SAA levels in RA patients with AA amyloidosis, which improves rheumatoid inflammation. ETN did benefit both RA inflammation and AA amyloidosis. This result suggests that the earlier the intervention with biologics, the better the outcome for patients. Tocilizumab also demonstrates excellent suppression of SAA levels and may have potential as a therapeutic agent for AA amyloidosis. Abatacept (ABT) also does efficacy and safety in AA amyloidosis secondary to RA. Because the gradual decrease in regulatory T-cells population coincides with AA amyloid deposit regression during ABT therapy, AA amyloid fibril turnover may involve an immunologic mechanism. Phagocytes seems to have an important role in AA amyloid regression, which suggests an immunologic interaction. Despite highly effectiveness of these biologics for rheumatoid inflammation, it is unclear whether the efficacy of biologics is present for AA amyloidosis. In particular, it is hard to evaluate the usefulness of biologics towards an amelioration of renal dysfunction.

### W61-6

#### Clinical feature of 103 pregnancies complicated with connective tissue disease in our institution

Hiromi Shimada, Kentaro Susaki, Tomohiro Kameda, Miharu Izumikawa, Yohei Takeuchi, Shusaku Nakashima, Hiroki Ozaki, Risa Wakiya, Hiroaki Dobashi

Department of Internal Medicine, Division of Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University

Conflict of interest: None

[Objective] We examine the issue of pregnancy and delivery complicated with connective tissue diseases by the analysis of the cases in our institution. [Method] We investigated 103 cases retrospectively; exacerbation of underlying disease, anti SS-A antibody, antiphospholipid antibody, preterm birth and abortion, neonatal birth weight, perinatal complication and dose of corticosteroid treatment. [Result] In 15 cases among all cases underlying diseases were exacerbated, and they need to strengthen their original therapies. 7 needed corticosteroid pulse therapies. In SLE (18.9%) and MCTD (25.0%) disease activities were more exacerbated during pregnancy. Positive anti SS-A antibody was found in 51.5% of all cases, and there was no complication related with its antibody. Among the cases of positive antiphospholipid antibodies, one had a preterm birth. There was a relationship between dose of corticosteroid and birth weight, delivery week, but they were also related with the exacerbation of underlying disease. Preterm birth, light for date and perinatal complication tended to arise in SLE, antiphospholipid syndrome and MCTD. [Conclusion] In pregnancy complicated with CTD, we need to control the disease activity strictly during pregnancy and delivery on each disease.

## W62-1

### DNA microarray analysis of labial salivary glands in patients with Sjögren's syndrome

Hiroyuki Takahashi<sup>1</sup>, Hiroto Tsuboi<sup>1</sup>, Mana Iizuka<sup>1</sup>, Hiromitsu Asashima<sup>1</sup>, Tomoya Hirota<sup>1</sup>, Yuya Kondo<sup>1</sup>, Masafumi Moriyama<sup>2</sup>, Sachiko Furukawa<sup>2</sup>, Isao Matsumoto<sup>1</sup>, Toshio Yoshihara<sup>3</sup>, Seiji Nakamura<sup>2</sup>, Takayuki Sumida<sup>1</sup>  
<sup>1</sup>Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan, <sup>2</sup>Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University, Fukuoka, Japan, <sup>3</sup>Department of Otolaryngology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Objectives] To clarify gene expression in labial salivary glands (LSGs) of Sjögren's syndrome (SS) with IgG4-related disease (IgG4-RD) and to identify genes involved in the pathogenesis of SS. [Methods] 1) Gene expression was analyzed by DNA microarray in LSGs of SS (n=5), IgG4-RD (n=5) and healthy controls (n=3). Differentially expressed genes (DEGs) in SS were identified. 2) Validation of the result was performed by quantitative PCR using LSGs from SS (n=11), IgG4-RD (n=11) and controls (n=3). 3) The protein production of validated genes in LSGs from SS (n=3) and IgG4-RD (n=1) was examined by indirect immunofluorescence assay. [Results] 1) In SS, 1320 up-regulated genes were identified as DEGs (false discovery rate <0.05) in comparison with IgG4-RD. 2) CXCL9, NR4A2, DPP4, SGK1, and PDK1 were selected as candidate genes for validation, according to rank<150, high expression levels, small variance, relation to T cell functions. PCR validated significantly higher expression of NR4A2 and DPP4 in SS than in IgG4-RD ( $P<0.05$ ). 3) Immunofluorescence staining in LSGs revealed higher production of NR4A2 in SS than in IgG4-RD and localization of NR4A2 dominantly in CD4<sup>+</sup>T cells of SS. [Conclusion] The results suggest that NR4A2 is a novel molecule involved in the pathogenesis of SS.

## W62-2

### Distinct Serum Protein Signature and Novel Biomarkers of primary Sjögren's Syndrome Revealed by comprehensive High-Throughput Proteomic Analysis

Ayumi Nishikawa<sup>1</sup>, Katsuya Suzuki<sup>1</sup>, Yoshiaki Kassai<sup>2</sup>, Yuumi Goto<sup>2</sup>, Takahiro Miyazaki<sup>2</sup>, Maiko Takiguchi<sup>2</sup>, Masaru Takeshita<sup>1</sup>, Atsuko Murota<sup>1</sup>, Rimpei Morita<sup>3</sup>, Tsutomu Takeuchi<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, <sup>2</sup>Takeda Pharmaceutical Company Limited, <sup>3</sup>Department of Microbiology and Immunology, Keio University School of Medicine

Conflict of interest: Yes

[Objectives] ESSDAI is used as an objective evaluation method of clinical disease activity in pSS. However, a useful substitute serum biomarker of disease activity has not been established. We aimed to reveal a distinct serum protein signature and novel biomarkers of pSS. [Methods] We studied 90 serum samples from 30 pSS patients, 30 RA patients, and 30 HC subjects. 1128 proteins were measured by comprehensive high-throughput proteomics assay. Associations between protein concentrations, clinical indicators and laboratory test results were statistically analyzed. [Results] We screened differentially up- and down-regulated proteins among the 3 groups, 195 proteins were statistically extracted. 60 proteins were up-regulated in pSS compared with HC. Enrichment analysis for characterization of up-regulated genes identified these as cytokines and chemokines and coagulation factors, indicating a serum protein signature in pSS. Multivariate analysis of these 60 proteins and ESSDAI identified 15 proteins with a statistically positive correlation, including TNF-associated molecules, and others. [Conclusion] This comprehensive proteomics analysis highlighted a dysregulated immunity and coagulation signature in patients with pSS. 15 proteins were found to be correlated with disease activity.

## W62-3

### Integrated comprehensive analysis of immune cell subsets and serum protein profile identifies the role of pre-germinal center B cells in Sjögren's syndrome pathogenesis

Yoshiaki Kassai<sup>1</sup>, Katsuya Suzuki<sup>2</sup>, Rimpei Morita<sup>3</sup>, Maiko Takiguchi<sup>1</sup>, Rina Kurisu<sup>1</sup>, Takahiro Miyazaki<sup>1</sup>, Tsutomu Takeuchi<sup>2</sup>

<sup>1</sup>Inflammation Drug Discovery Unit, Takeda Pharmaceutical Company Limited, Kanagawa, Japan, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, <sup>3</sup>Department of Microbiology and Immunology, Keio University School of Medicine, Tokyo, Japan

Conflict of interest: Yes

[Objectives] We performed comprehensive flow cytometric analysis by multi-colored staining in combination with serum protein profile to fully understand pathophysiological aspects in rheumatoid arthritis (RA) and primary Sjögren's syndrome (pSS). [Methods] Peripheral blood and serum was collected from untreated RA patients (N = 51), pSS patients (N = 60), and healthy controls (N = 36). [Results] Among over 40 immune cell subsets we investigated, surface IgD<sup>+</sup> CD38<sup>++</sup> B cells, called pre-germinal center B (pre-GC B), were significantly increased in both RA and pSS patients. Interestingly, serum IgG was positively correlated with the number of pre-GC B cells in pSS but not RA, suggesting their distinct role in pSS pathogenesis. Consistent with this, several GC-related serum proteins focused by SOMAscan were significantly elevated and correlated with pre-GC B in pSS but not RA. Furthermore, pre-GC B cells isolated from pSS exhibited higher GC-related gene expressions including *XBPI* and *BACH2* than those from healthy controls. [Conclusion] Our findings suggest possible role of pre-GC B in pSS pathogenesis through IgG production and germinal center formation. This integrated strategy is a useful tool to highly impact on better understanding of autoimmune diseases.

## W62-4

### Direct HTLV-I infection toward salivary glands epithelial cells and expression of relevant molecules in primary Sjögren's syndrome

Hideki Nakamura<sup>1</sup>, Yoshiko Takahashi<sup>1</sup>, Tomomi Yamamoto-Fukuda<sup>2</sup>, Yoshiro Horai<sup>1</sup>, Yoshikazu Nakashima<sup>1</sup>, Kazuhiko Arima<sup>3</sup>, Takehiko Koji<sup>2</sup>, Atsushi Kawakami<sup>1</sup>

<sup>1</sup>Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, <sup>2</sup>Department of Histology and Cell Biology, Unit of Basic Medical Science, Nagasaki University Graduate School of Biomedical Sciences, <sup>3</sup>Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, <sup>4</sup>Department of Social Work, Faculty of Human and Social Studies, Nagasaki International University

Conflict of interest: None

**Objectives:** To examine infection of HTLV-I toward salivary glands epithelial cells (SGECs) and expression of relevant molecules in primary Sjögren's syndrome (pSS) in vitro. **Methods:** Cytokine and apoptosis array were used for samples from co-culture between SGEC of SS patients and HCT-5/Jurkat. Expression of HTLV-I-related protein was examined by IF or WB. Expression of HTLV-I proviral DNA was determined by in situ PCR by using HTLV-I pX region primers. **Results:** HTLV-I-related proteins were detected with p65 nuclear translocation at 72-96 co-culture with HCT-5. HTLV-I-related proteins and cytokeratin-double positive SGECs were  $7.8 \pm 1.3$  %. HTLV-I proviral DNA was detected at 48 hour co-culture by in situ PCR. ICAM-1, RANTES or interferon gamma-induced protein 10kDa (IP-10/CXCL10) were observed in supernatant co-cultured with HCT-5. However, no increase of these molecules was observed in supernatant co-cultured with Jurkat. Pro-apoptotic molecules such as cytochrome C and Fas and anti-apoptotic molecules including Bcl-2, HO-2, HSP-27 were detected in SGEC lysate co-cultured with HCT-5, although no TUNEL staining was observed during 0-96 hour co-culture. **Conclusion:** Direct infection of HTLV-I toward SGEC was partly detected in vitro with up-regulation of associated molecules.

## W62-5

### Hereditary angioedema in Japan: association with autoimmune disorders like Sjogren's syndrome

Makiko Maekawa<sup>1</sup>, Yasutaka Kimoto<sup>1</sup>, Shigeru Yoshizawa<sup>2</sup>, Yojiro Arinobu<sup>3</sup>, Hideaki Goda<sup>1</sup>, Yoshihiro Higuchi<sup>1</sup>, Yoshiyuki Arita<sup>1</sup>, Hiroaki Niuro<sup>3</sup>, Hiroshi Tsukamoto<sup>3</sup>, Takahiko Horiuchi<sup>1</sup>

<sup>1</sup>Kyushu University Beppu Hospital, Beppu, Japan, <sup>2</sup>National Hospital Organization Fukuoka Hospital, Fukuoka, Japan, <sup>3</sup>Kyushu University Hospital, Fukuoka, Japan

Conflict of interest: None

[Objectives] Hereditary angioedema (HAE) is an autosomal inherited disorder caused by mutations in C1-inhibitor gene (*C1-INH*). HAE sometimes associated with autoimmune disorders such as Sjogren's syndrome (SjS). We aimed to clarify the features of HAE in Japan, which is still not well investigated. [Methods] We searched the literature from January 1969 through October 2010 on Japanese patients with HAE. Genetic analysis was performed by PCR followed by direct sequencing and MLPA. [Results] Of the 132 reported patients, 91 (69%) were female. Of the 80 patients with a known phenotype, 87.5% had type 1 and 12.5% had type 2. Of these 109 patients with documentation of family history, 24 (22%) did not have a family history of HAE. Eight HAE patients were associated with SLE and 3 had SjS. The clinical and genetic data of our two HAE patients with SjS are presented. Both were female and were positive for ANA, anti-SS-A Ab and anti-SS-B Ab. Complement CH50 and C4 were decreased to almost undetectable levels. One amino acid substitution and a large deletion of C1-INH gene was identified in each of the patient. [Conclusion] Complement deficiency secondarily caused by HAE might be a risk factor for autoimmune disorders, such as SLE and SjS.

## W62-6

### Anti-CCP antibody-positive articular symptoms in Sjogren's syndrome: long-term follow-up of 9 cases

Yasunori Suzuki, Hiroshi Fujii, Kazunori Yamada, Mitsuhiko Kawano  
Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

Conflict of interest: None

Objective: It is sometimes difficult to definitively differentiate between articular involvement in primary Sjogren's syndrome (SS) and an overlap of SS and rheumatoid arthritis (RA), despite a positive anti-CCP antibody (ACPA) test. We analyzed long-term follow-up data on ACPA-positive arthralgia and arthritis in SS. Method: We retrospectively studied 9 patients with SS diagnosed with the Japanese criteria and/or ACR criteria who showed articular symptoms with ACPA positivity. RA was diagnosed by rheumatologists, and all cases met the ACR/EULAR criteria. Results: The patients were 8 women and 1 man (mean age, 44 ± 12 years). The mean follow-up period was 69 ± 47 months. The final diagnosis was primary SS in 5 cases, osteoarthritis in 1, and an overlap of SS and RA in 3. The 5 cases of primary SS showed arthralgia or temporary arthritis, and no patients showed joint destruction. Three cases with SS and RA overlap showed no significant difference in clinical data on SS compared with 5 primary SS cases. Two of 3 cases were treated with biologics. Conclusion: Articular symptoms in SS patients cannot be diagnosed as an overlap with RA at a single time point despite ACPA positivity. ACPA-positive SS needs close follow-up instead of immediately concluding a diagnosis of RA overlap.

## W63-1

### The serum albumin value is useful in order to evaluate the disease activity of rheumatoid arthritis

Masahiko Miya  
Komoro Kosei General Hospital, Komoro, Japan

Conflict of interest: None

[Objectives] Changing serum albumin value in connection with chronic inflammation is known for rheumatoid arthritis. Correlation of DAS28-CRP disease activity and a serum albumin value is considered,

and the usefulness of the serum albumin value in disease activity evaluation is examined. [Methods] In 4869 data of 113 rheumatoid arthritis patients, a correlation between serum albumin value and DAS28-CRP disease activities were considered. [Results] The DAS28-CRP score and the serum albumin value accepted correlation. The correlation coefficient was -0.36. When serum albumin was 2.8 g/dl, DAS28 score was an average of 5.1, and when a serum albumin value was 4.8 g/dl, DAS28 score was an average of 2.0. With the cases whose serum albumin value was 2.8 g/dl, all the members' disease activity was either high or moderate. With the case whose serum albumin value was 4.8 g/dl, all the members' disease activity was either low or remission. [Conclusion] Albumin is biosynthesized in liver and metabolism is promoted by inflammatory cytokine, such as IL-6. Therefore, inflammatory disorders, such as rheumatoid arthritis, cause hypoalbuminemia. The serum albumin value is useful as a disease activity index of rheumatoid arthritis.

## W63-2

### Relationship Between Time Up to Go and Physical Function in Patients with Long-Standing Rheumatoid Arthritis: Multicenter Prospective Cohort Study for Evaluation of Joint Surgery on Physical Function

Toshihisa Kojima<sup>1</sup>, Hajime Ishikawa<sup>2</sup>, Keiichiro Nishida<sup>3</sup>, Jun Hashimoto<sup>4</sup>, Hisaaki Miyahara<sup>5</sup>, Sakae Tanaka<sup>6</sup>, Nobuhiko Haga<sup>7</sup>, Yasuo Niki<sup>8</sup>, Masayo Kojima<sup>9</sup>, Naoki Ishiguro<sup>1</sup>

<sup>1</sup>Orthopedic Surgery, Nagoya University Hospital, Nagoya, Japan, <sup>2</sup>Orthopedic Surgery, Niigata Rheumatic Center, Niigata, Japan, <sup>3</sup>Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, <sup>4</sup>Rheumatology, National Hospital Organization Osaka Minami Medical Centre, Osaka, Japan, <sup>5</sup>Orthopedic Surgery, National Hospital Organization Kyushu Medical Centre, Fukuoka, Japan, <sup>6</sup>Orthopaedic Surgery and Spinal Surgery, The University of Tokyo Hospital, Tokyo, Japan, <sup>7</sup>Rehabilitation Medicine, The University of Tokyo Hospital, Tokyo, Japan, <sup>8</sup>Orthopedic Surgery, Keio University School of Medicine, Tokyo, Japan, <sup>9</sup>Public Health, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Conflict of interest: Yes

[Objectives] The purpose of this study is to explore the characteristics of functional impairment and relationship Time Up to Go (TUG) and physical function in RA patients who were needed joint surgery using multicenter prospective cohort. [Methods] We started the prospective study in September, 2012. We collected data on age, sex, disease duration, drug therapies, and disease activity. Functional evaluations were made using the TUG, HAQ-DI, DASH (upper limb function), and patient subjective evaluations using the EQ-5D (QOL) and BDI-II (depression). Joint range of motion was also measured as part of this evaluation. [Results] 347 surgical patients were registered. Mean values for age, disease duration, and sex were 65.2 years, 18 years, and 88% female, respectively. Disease activity of even long-standing RA patients in this study was under control (median values for DAS28 (3.0)). We confirmed the significant correlation between TUG and disease duration, HAQ-DI, EQ-5D, BDI-II and range of motion (hip, knee, shoulder ankle). Cut-off value of TUG for high ADL status (total HAQ point <6/60) was 8.98 seconds. [Conclusion] TUG was significantly associated with many kinds of daily activity and patient-reported outcome. TUG as shown in this study could be target of surgical procedure.

## W63-3

### Effect of biological DMARDs on microstructure damage in the cartilage of patients with rheumatoid arthritis (1 year follow up evaluation by T1ρ and T2 mapping)

Jun Hirose<sup>1</sup>, Hiroaki Nishioka<sup>1</sup>, Hiroshi Mizuta<sup>1</sup>, Michishi Tsukano<sup>2</sup>, Saburo Matsubara<sup>3</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Kumamoto University Hospital, Kumamoto, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Kumamoto Orthopaedic Hospital, Kumamoto, Japan, <sup>3</sup>Center for Arthritis and Clinical Rheumatology, Matsubara Clinic

Conflict of interest: None

[Objectives] To study microstructural change in the cartilage of pa-

tients with rheumatoid arthritis (RA) during 1 year therapy of biological disease modifying antirheumatic drugs (DMARDs), we evaluated knee cartilage using T1 $\rho$  and T2 MRI mapping. [Methods] Sagittal T1 $\rho$  maps of the femorotibial joint were obtained in 13 RA patients. Four regions of interest (ROIs) were placed on images of the cartilage in the medial and lateral femoral condyle (MFC, LFC) and the medial and lateral tibia plateau (MT, LT). The T1 $\rho$  and T2 values (ms) of each ROI were recorded before and 1 year after starting biological DMARDs, and their changes were evaluated. [Results] The % increase of T1 $\rho$  in four condyles were 3.4, 3.3, 0.6, 1.0 and those of T2 were 5.1, 3.6, 3.0, 6.8, respectively. The changes of T1 $\rho$  significantly correlated with DAS28 in the MFC, body weight and swollen and tender joint counts in the LFC, and disease duration in the MT. [Conclusion] Microstructure damage in the knee cartilage increases even though clinical remission was achieved in RA patients. These changes may be associated with the arthritis status before starting biologic therapy.

#### W63-4

##### **Pathological Change Caused by Biologics in Rheumatoid Arthritis Synovial Tissue — Consideration of Cases with Multiple Surgeries Performed —**

Ayako Kubota<sup>1</sup>, Masayuki Sekiguchi<sup>1</sup>, Takashi Nakamura<sup>1</sup>, Yoshiyasu Miyazaki<sup>1</sup>, Ryo Takamatssu<sup>1</sup>, Toyomitsu Tsuchida<sup>2</sup>, Toru Suguro<sup>3</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Toho University School of Medicine, Tokyo, Japan, <sup>2</sup>Tsuchida Clinic, <sup>3</sup>Japan Research Institute of Artificial Joint

Conflict of interest: None

[Objectives] We examined biologics on RA synovial tissue using pathological findings collected from the same patient during multiple surgeries performed. [Methods] Surgeries were performed for 11 cases of RA with biologics at our department from 2006 to 2014. ETN, IFX, and TCZ was used for 9, 1 and 1 case respectively. Disease activity was assessed by DAS 28-ESR and CDAI. Pathological findings were examined by Rooney score and inflammation score defined as one excepting those in items of number of vessels and fibrosis. [Results] With improvement observed between before and after surgery from 4.4 to 3.5 in DAS 28-ESR and 17.1 to 11.9 in CDAI, significant difference was not recognized. Rooney score decreased from 14.3 to 14.7 and inflammation score from 8.9 to 8.7 showing no significant difference. CDAI in 3 and 8 joints at the time of last surgery was low and moderate respectively. Inflammation score decreased to low value in low group showing significant difference. Lymphocytic infiltration in sub-lining tissue remained in 37.5% (three joints) showing high value in inflammatory score in moderate group. [Conclusion] It is believed surgical treatment is required even for cases with better therapeutic response for biologics because of existence of remaining synovitis in some cases.

#### W63-5

##### **Analysis of 68 joints score in comparison with 28 joints score in rheumatoid arthritis**

Moritoshi Furu<sup>1</sup>, Motomu Hashimoto<sup>1</sup>, Takao Fujii<sup>1,2</sup>, Hiromu Ito<sup>1,3</sup>, Masahiro Ishikawa<sup>1,3</sup>, Noriyuki Yamakawa<sup>2</sup>, Chikashi Terao<sup>4</sup>, Wataru Yamamoto<sup>6</sup>, Hiroyuki Yoshitomi<sup>3,5</sup>, Hiroko Ogino<sup>3</sup>, Shuichi Matsuda<sup>3</sup>, Tsuneyo Mimori<sup>1,2</sup>

<sup>1</sup>Department of the Control for Rheumatic Diseases, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>2</sup>Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>3</sup>Department of Orthopaedic Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>4</sup>Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>5</sup>Center for Innovation in Immunoregulative Technology and Therapeutics, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>6</sup>Kurashiki Sweet Hospital, Okayama, Japan

Conflict of interest: Yes

[Objectives] Many of disease activity scores in rheumatoid arthritis (RA) have been simplified to 28 joint counts. Symptom in 66/68 joints other than 28 joints may result in radiological progression. The aim of this study was to clarify discrepancy of clinical data between 28 joint

counts and 66/68 joint counts. [Methods] We chose the 370 of consecutive RA patients, with 2012 RA survey in our observational cohort, and assessed clinical variables. We compared two groups, with or without symptom in 66/68 joints without 28 joints, and search prognosis factors for remaining symptom in joints other than 28 joints. [Results] Symptom in joints other than 28 joints was observed in 97 patients (26.2%), and 94% of symptom was feet. There were significant higher stage, class, HAQ-DI, and mTSS with symptom than without symptom in 66/68 joints other than 28 joints. Prognosis factors for remaining symptom in joints other than 28 joints were no-usage of biologics (OR8.51, p<0.01), higher PtGH (OR1.05, p=0.01), younger age (OR1.05, p=0.03), and higher mTSS (OR1.01, p=0.03). [Conclusion] Most of symptom in joints other than 28 joints was observed in feet. Prognosis factors for remaining symptom in joints other than 28 joints were no-usage of biologics, higher PtGH, younger age, and higher mTSS.

#### W63-6

##### **Correlation between thyroid function and disease activities in patients with rheumatoid arthritis**

Hideaki Tsuji<sup>1</sup>, Motomu Hashimoto<sup>2</sup>, Takao Fujii<sup>2</sup>, Masahiro Ishikawa<sup>2</sup>, Moritoshi Furu<sup>2</sup>, Hiromu Ito<sup>2,3</sup>, Kosaku Murakami<sup>1</sup>, Ran Nakashima<sup>1</sup>, Yoshitaka Imura<sup>1</sup>, Naoichiro Yukawa<sup>1</sup>, Hajime Yoshifuji<sup>1</sup>, Koichiro Ohmura<sup>1</sup>, Tsuneyo Mimori<sup>1,2</sup>

<sup>1</sup>Department of Rheumatology and Clinical Immunology, Kyoto University Hospital, Kyoto, Japan, <sup>2</sup>Department of the Control for Rheumatic Diseases, Kyoto University Hospital, Kyoto, Japan, <sup>3</sup>Department of Orthopedic Surgery, Kyoto University Hospital, Kyoto, Japan

Conflict of interest: None

[Objectives] Triiodothyronine (T<sub>3</sub>) can be decreased in debilitating condition (low T<sub>3</sub> syndrome, or euthyroid sick syndrome: ESS). We investigated thyroid function and activity of rheumatoid arthritis (RA). [Methods] We analyzed thyroid function in 366 RA patients from 2011 to 2014, and checked thyroid antibodies in patients with abnormal thyroid function. We investigated association between thyroid function and disease activity in ESS group who showed low fT<sub>3</sub> but no thyroid antibodies. [Results] Seventy six out of 366 RA patients (20.8%) showed abnormal thyroid function (hyperthyroid: 15, hypothyroid: 29, abnormal TSH: 32 cases). In 76 patients with abnormal thyroid function, thyroid antibodies were positive in 11 cases (14%). In 42 cases whose thyroid function was followed up,  $\Delta$ DAS28,  $\Delta$ Hb,  $\Delta$ Alb and  $\Delta$ CRP were correlated with  $\Delta$ fT<sub>3</sub>, but not with  $\Delta$ fT<sub>4</sub>. Twenty cases (5%) were classified as ESS. DAS28, MMP-3, IgG, ESR, and CRP were higher, and Hb, Alb, and ChE were lower in ESS group than those with normal thyroid function (290 cases). During the course, along with improvement of RA, fT<sub>3</sub> level normalized in 65% in ESS group. [Conclusion] RA patients with low levels of fT<sub>3</sub> showed higher disease activities and wasting conditions. fT<sub>3</sub> levels were correlated with activities of RA.

#### W64-1

##### **Association study of LILRA4 with systemic lupus erythematosus**

Aya Kawasaki<sup>1</sup>, Hiroshi Furukawa<sup>2</sup>, Yuya Kondo<sup>3</sup>, Satoshi Ito<sup>4</sup>, Isao Matsumoto<sup>3</sup>, Makio Kusaoi<sup>5</sup>, Hirofumi Amano<sup>5</sup>, Akiko Suda<sup>6,7</sup>, Shohei Nagaoka<sup>6</sup>, Keigo Setoguchi<sup>8</sup>, Tatsuo Nagai<sup>9</sup>, Shunsei Hirohata<sup>9</sup>, Kota Shimada<sup>10</sup>, Shoji Sugii<sup>10</sup>, Akira Okamoto<sup>11</sup>, Noriyuki Chiba<sup>12</sup>, Eiichi Suematsu<sup>13</sup>, Shigeru Ohno<sup>7</sup>, Masao Katayama<sup>14</sup>, Akiko Okamoto<sup>15</sup>, Hajime Kono<sup>15</sup>, Yoshinari Takasaki<sup>5</sup>, Hiroshi Hashimoto<sup>16</sup>, Takayuki Sumida<sup>3</sup>, Shigeto Tohma<sup>2</sup>, Naoyuki Tsuchiya<sup>1</sup>

<sup>1</sup>Molecular and Genetic Epidemiology, University of Tsukuba, Tsukuba, Japan, <sup>2</sup>Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara National Hospital, Sagamihara, Japan, <sup>3</sup>Department of Internal Medicine, University of Tsukuba, Tsukuba, Japan, <sup>4</sup>Niigata Rheumatic Center, Shibata, Japan, <sup>5</sup>Department of Internal Medicine and Rheumatology, Juntendo University, Tokyo, Japan, <sup>6</sup>Department of Rheumatology, Yokohama Minami Kyosai Hospital, Yokohama, Japan, <sup>7</sup>Center for Rheumatic Diseases, Yokohama City University Medical Center, Yokohama, Japan, <sup>8</sup>Allergy and Immunological Diseases, Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan, <sup>9</sup>Department of Rheumatology and Infectious Diseases, Kitasato University, Sagamihara, Japan, <sup>10</sup>Department of Rheumatology, Tama Medical Center, Tokyo, Japan, <sup>11</sup>Department of Rheumatology, Himeji



Medical Center, Himeji, Japan, <sup>12</sup>Department of Rheumatology, Morioka Hospital, Morioka, Japan, <sup>13</sup>Department of Internal Medicine and Rheumatology, Kyushu Medical Center, Fukuoka, Japan, <sup>14</sup>Department of Internal Medicine, Nagoya Medical Center, National Hospital Organization, Nagoya, Japan, <sup>15</sup>Department of Internal Medicine, Teikyo University, Tokyo, Japan, <sup>16</sup>School of Medicine, Juntendo University, Tokyo, Japan

Conflict of interest: None

[Objectives] *Leukocyte immunoglobulin (Ig)-like receptor (LILR)* multigene family are clustered on human chromosome 19q13.4. LILRA4 is thought to negatively regulate production of type I interferons, which are involved in the pathogenesis of systemic lupus erythematosus (SLE). In this study, we examined whether *LILRA4* polymorphisms are associated with SLE. [Methods] An association study of 12 tag SNPs in the *LILRA4* region was conducted in 501 Japanese patients with SLE and 551 healthy controls. A replication study was carried out in 338 SLE and 265 healthy controls. [Results] Among the 12 tag SNPs, rs7259036, located downstream of the *LILRA4* gene, showed the strongest association with SLE ( $P=3.8 \times 10^{-4}$ , odds ratio [OR]: 1.61). We next examined the association of rs7259036 using an independent SLE and control set. Significant association was not observed in the replication study ( $P=0.73$ , OR: 1.06). When the two studies were combined by a meta-analysis, rs7259036A was slightly increased in SLE, although the difference did not reach statistical significance ( $P=0.18$ , OR: 1.33). [Conclusion] Although tendency towards association was observed between *LILRA4* and SLE, further studies with larger sample size are required to draw a conclusion.

#### W64-2

##### Association of single nucleotide polymorphisms of the *BACH2* gene with susceptibility to systemic lupus erythematosus

Mari Tochihiro, Manabu Kawamoto, Kae Takagi, Yasuhiro Katsumata, Hisae Ichida, Akiko Tochimoto, Masanori Hanaoka, Yuko Okamoto, Hidenaga Kawasumi, Yasushi Kawaguchi, Hisashi Yamanaka  
Institute of Rheumatology Tokyo Women's Medical University

Conflict of interest: None

[Objectives] The aim of this study was to investigate the association of gene polymorphisms of *BACH2* with susceptibility to SLE. [Background] Many studies have demonstrated the impairment of several transcription factors in SLE. We focused on the *BACH2* gene which is a transcription factor. *BACH2* is expressed at a high level in B cells and has a function about differentiation of B cells. *BACH2* has several functions in both acquired and innate immunity. Although the previous studies have shown an association between *BACH2* gene and various autoimmune diseases, it is unclear whether the *BACH2* gene may be associated with SLE. [Methods] We genotyped rs11755527 and rs3757247 in the *BACH2* gene from 245 patients with SLE by TaqMan assay. And then, we compared them with control subjects with Fisher's exact test. [Results] The frequency of carrying C allele at the rs11755527 was significantly higher in SLE than that in controls ( $p = 0.023$ ). A genotypic study at rs11755527 suggested that C/C and C/G genotypes indicated the higher frequency than G/G genotype ( $p = 0.048$ ). Regarding as rs3757247, the frequency of C allele was significantly higher in SLE than that in controls ( $p=0.033$ ). [Conclusion] We found that the *BACH2* gene was the one of susceptibility genes to SLE in the Japanese.

#### W64-3

##### Clarification of the role of FcγRIIB for *Yaa*-related lupus nephritis by establishing the cell type-specific FcγRIIB deficient mice

Qingshun Lin<sup>1</sup>, Keiko Nishikawa<sup>1</sup>, Mareki Ohtsuji<sup>3</sup>, Hirofumi Amano<sup>2</sup>, Hiroyuki Nishimura<sup>3</sup>, Toshikazu Shirai<sup>1</sup>, Sachiko Hirose<sup>1</sup>

<sup>1</sup>Department of Pathology, Juntendo University School of Medicine, Tokyo, Japan, <sup>2</sup>Department of Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan, <sup>3</sup>Toin Human Science and Technology Center, Department of Biomedical Engineering, Toin University of Yokohama, Yokohama, Japan

Conflict of interest: None

[Objectives] We examined the role of FcγRIIB for the pathogenesis

of lupus nephritis in cell type-specific manner. [Methods] We established cell-type specific FcγRIIB-deficient B6 mice carrying *Yaa*, namely B cell-specific (CD19<sup>Cre</sup>.*Yaa*), myeloid cell-specific (C/EBPα<sup>Cre</sup>.*Yaa*), and DC-specific (CD11c<sup>Cre</sup>.*Yaa*) mice, and compared disease phenotypes with those in full-deficient FcγRIIB<sup>mut</sup>.*Yaa* mice. [Results] FcγRIIB<sup>mut</sup>.*Yaa* developed severe lupus nephritis with high serum autoantibody levels, while lupus nephritis in CD19<sup>Cre</sup>.*Yaa* was markedly suppressed. C/EBPα<sup>Cre</sup>.*Yaa* also developed lupus nephritis, the findings comparable to those in CD19<sup>Cre</sup>.*Yaa*. CD11c<sup>Cre</sup>.*Yaa* did not develop the disease. In peripheral blood, the frequencies of activated Gr1<sup>+</sup>FcγRIV<sup>+</sup> monocytes were increased in FcγRIIB<sup>mut</sup>.*Yaa* and C/EBPα<sup>Cre</sup>.*Yaa*, lacking FcγRIIB expression on monocytes. There was no strain difference in the frequencies of neutrophils. [Conclusion] Severe lupus nephritis in FcγRIIB<sup>mut</sup>.*Yaa* was not simply explained by the FcγRIIB deficiency on B cells. The lack of FcγRIIB expression on B cells and monocytes may contribute to autoantibody production via B cell autonomous activation and monocyte-mediated mechanism, respectively.

#### W64-4

##### The ubiquitylation of IRF family is reduced in patients with systemic lupus erythematosus

Reikou Kamiyama<sup>1</sup>, Ryusuke Yoshimi<sup>1</sup>, Daiga Kishimoto<sup>1</sup>, Mitsuhiro Takeno<sup>1</sup>, Atsuhisa Ueda<sup>1</sup>, Keiko Ozato<sup>2</sup>, Yoshiaki Ishigatsubo<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, <sup>2</sup>Program in Genomics of Differentiation, Eunice Kennedy Shriver National Institute of Child Health and Human Development

Conflict of interest: None

[Objectives] TRIM21 has been suggested to have the E3 ubiquitin ligase activity, and the corresponding antibodies are detected in serum of patients with systemic lupus erythematosus (SLE). Here we investigated the role of TRIM21 in SLE pathogenesis. [Methods] We collected peripheral blood mononuclear cells from 20 patients with SLE and 24 healthy controls (HC) and analyzed the expression levels of TRIM21, type I interferons (IFNs) and IFN regulatory factors (IRFs). We compared the ubiquitylation of IRFs between SLE and HC. The effect on relationship between TRIM21 and type I IFN production caused by disease activity or anti-TRIM21 antibodies was also investigated. [Results] The mRNA and protein levels of TRIM21 were significantly higher in SLE as compared to HC, and the TRIM21 mRNA level correlated with disease activity. The ubiquitylation of IRF family declined in SLE. Although the mRNA levels of type I IFNs showed negative correlations with TRIM21 mRNA level in HC, these correlations were not observed in SLE. In patients with anti-TRIM21 antibodies, a positive correlation between type I IFN and TRIM21 mRNA expressions was observed. [Conclusion] These results suggest that the malfunction of TRIM21 as an E3 ligase for IRF family may be involved in the pathogenesis of SLE.

#### W64-5

##### Molecular mechanisms of impaired induction of regulatory B cells in autoimmune diseases

Shun-ichiro Ota<sup>1</sup>, Hiroaki Niirō<sup>2</sup>, Naoko Ueki<sup>1</sup>, Yuri Hirosaki<sup>1</sup>, Tsuyoshi Nakayama<sup>1</sup>, Shoichiro Inokuchi<sup>1</sup>, Ayako Takaki<sup>1</sup>, Koji Mishima<sup>1</sup>, Shota Nakano<sup>1</sup>, Jin Nakagawa<sup>1</sup>, Daisuke Oryoji<sup>1</sup>, Masahiro Ayano<sup>1</sup>, Sho Ueda<sup>1</sup>, Satomi Hisamoto<sup>1</sup>, Atsushi Tanaka<sup>1</sup>, Hiroki Mitoma<sup>1</sup>, Mitsuteru Akahoshi<sup>1</sup>, Yojiro Arinobu<sup>1</sup>, Hiroshi Tsukamoto<sup>1</sup>, Koichi Akashi<sup>1</sup>

<sup>1</sup>Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Japan, <sup>2</sup>Clinical Education Center, Kyushu University Hospital

Conflict of interest: None

[Objectives] We previously showed that TLR9-mediated Breg induction is impaired in systemic lupus erythematosus (SLE). In the present study we have sought to elucidate the underlying mechanism of this phenomenon in SLE. [Methods] Expression of mRNAs and proteins in B cells was assessed by quantitative PCR, ELISA and flow cytometry. Bregs were co-cultured with T cells, and proliferation and IFNγ production of T cells were tested. The knock-down vector of Blimp-1 was generated and transfected into B cells. [Results] Positive correlation between

Blimp1 and IL-10 expression was noted in Bregs. Blimp1 silencing caused a remarkable suppression of Breg induction. Intriguingly, upon TLR9 stimulation IgM memory B cells expressed IL-10 more significantly than plasmablasts, a subset expressing the highest level of Blimp1. These suggest that the induction ratio of Blimp1, but not its levels, is critical for the efficiency of Breg induction. Consistent with this idea, the further induction of Blimp-1 by TLR9 stimulation was significantly abrogated, along with less IL-10 production in SLE. [Conclusion] Together, these findings provide not only a better understanding of molecular mechanisms of Breg induction in humans, but also a novel clue to revitalizing Bregs for the treatment of SLE.

## W64-6

### The role of immune regulation on CD4 + CD52 + T cells in systemic lupus erythematosus

Masataka Umeda<sup>1</sup>, Tomohiro Koga<sup>1</sup>, Kunihiro Ichinose<sup>1</sup>, Sosuke Tsuji<sup>1</sup>, Shoichi Fukui<sup>1</sup>, Ayako Nishino<sup>1</sup>, Yoshikazu Nakashima<sup>1</sup>, Takahisa Suzuki<sup>1</sup>, Yoshiro Horai<sup>1</sup>, Yasuko Hirai<sup>1</sup>, Shin-ya Kawashiri<sup>1</sup>, Naoki Iwamoto<sup>1</sup>, Toshiyuki Aramaki<sup>2</sup>, Mami Tamai<sup>1</sup>, Hideki Nakamura<sup>1</sup>, Tomoki Origuchi<sup>3</sup>, Yukitaka Ueki<sup>2</sup>, Atsushi Kawakami<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Unit of Translational Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan, <sup>2</sup>Sasebo Chuo Hospital, Nagasaki, Japan, <sup>3</sup>Department of Rehabilitation Sciences, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan

Conflict of interest: None

[Object] It has been suggested that CD52high T cells is involved in autoimmune diseases with different functions of regulatory T cells (Treg). The purpose of this study is to determine the role of immune regulation on CD4 + CD52 + T cells in systemic lupus erythematosus (SLE). [Methods] We isolated the human peripheral blood mononuclear cells (PBMC) of SLE patients: n=33, non SLE patients: n=8 (rheumatoid arthritis: n=6, mixed connective-tissue disease: n=2) and healthy controls (HC): n=11. The expression of CD4 + CD25 + CD127- cells (Treg) and CD52high and CD52low T cells were analyzed by flow cytometry. Correlation with clinical parameters including SLEDAI, anti-ds-DNA antibody titer or complement titer was also analyzed. [Results] No significant difference was noted in the percentage of CD4 + CD25 + CD127- cells among the three groups. There was no correlation between Treg and CD52low T cells in SLE. We found that CD52low T cells of SLE were significantly correlated with SLEDAI. CD52low T cells of SLE with high-SLEDAI (5>) was significantly higher than HC, non-SLE and SLE with low-SLEDAI (0-5). [conclusion] Collectively, our data indicates that the decreased CD4 + CD52low T cells may contribute to the development of SLE.

## W65-1

### Association of anti-NR2 and U1RNP antibodies with inflammatory mediators in cerebrospinal fluid from patients with neuropsychiatric systemic lupus erythematosus

Seiko Kondo-Ishikawa<sup>1</sup>, Takao Fujii<sup>2</sup>, Nozomi Ishigooka<sup>1</sup>, Kosaku Murakami<sup>1</sup>, Motomu Hashimoto<sup>2</sup>, Yoshitaka Imura<sup>1</sup>, Naoichiro Yukawa<sup>1</sup>, Hajime Yoshifuji<sup>1</sup>, Koichiro Ohmura<sup>1</sup>, Tsuneyo Mimori<sup>1</sup>

<sup>1</sup>Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Japan, <sup>2</sup>Department of the Control for Rheumatic Diseases, Graduate School of Medicine, Kyoto University, Japan

Conflict of interest: None

[Objectives] Autoantibodies (auto Abs) in cerebrospinal fluid (CSF) and inflammatory mediators (IMs) may be involved in the pathogenesis of neuropsychiatric SLE (NPSLE). In the present study, we examined CSF-anti-NR2, U1RNP Abs and IMs in CSF and determined their association with NPSLE. [Methods] We obtained CSF samples from 64 NPSLE and 13 non-NPSLE patients (control). CSF-anti-NR2 and U1RNP Abs were detected by ELISA and RNA-immunoprecipitation, respectively. CSF-IL-6, IL-8, MIG and IP-10 were measured by quantitative multiplex cytokine analysis. [Results] 1) CSF-IL-6 and IP-10 levels were higher in CSF-anti-NR2 Ab-positive patients than in -negative and

controls. CSF-MIG levels were higher in CSF-anti-U1RNP Ab-positive patients than in -negative and controls. 2) We divided our NPSLE patients into 4 groups: CSF-anti NR2 Ab +/-U1RNP-(NR2, 15 patients), CSF-anti-NR2-/U1RNP+(U1RNP, 8), double positive (DP, 7), double negative (DN, 34). In DP among 4 groups, active psychiatric manifestations were the most frequently observed and CSF-IL-6, MIG and IP-10 levels were the highest. 3) CSF-IL-8 level was strongly correlated to CSF-MIG. [Conclusion] We found the severest subset of NPSLE that showed both anti-NR2 and U1RNP Ab-positive and multiple IM activations in CSF.

## W65-2

### Association of anti-glutamate receptor subunit NR2 antibody and psychiatric disorder in patients with primary Sjögren syndrome

Yoshiyuki Arinuma, Yuko Sakuma, Nobuhiro Sho, Eisuke Ogawa, Tatsuhiro Wada, Tatsuo Nagai, Sumiaki Tanaka, Shunsei Hirohata  
Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine

Conflict of interest: None

[Objectives] Anti-glutamate receptor subunit NR2 antibody (anti-NR2) is one of the pathogenic autoantibodies related to psychiatric disorder (PD) in patients with systemic lupus erythematosus (SLE). Although PD, such as depression and anxiety, is relatively frequently observed, anti-NR2 in Sjögren syndrome (SjS) has not been clarified. The aim of this study is to investigate the association of anti-NR2 and PD in patients with primary SjS (pSjS). [Methods] We examined 31 patients with pSjS, 13 patients with rheumatic diseases other than SLE or SjS as disease control (DC) and 36 healthy individuals (HC). Anti-NR2 was measured by ELISA. [Results] The level of anti-NR2 in serum was significantly elevated in patients with pSjS (47.6±71.7U/ml), compared to those with DC (13.9±16.4, p=0.0115) or HC (16.8±9.6, p=0.0260). In pSjS patients with PD, the serum anti-NR2 level was significantly higher than those without PD (p=0.0014). Also, the positivity of anti-NR2 in serum was found to be a significant risk factor for PD in pSjS patients (OR 28.8, 95%CI 4.04-630.87, p=0.0041). The levels of anti-NR2 in cerebrospinal fluid from 3 pSjS patients with PD were increased above the cutoff value. [Conclusion] Anti-NR2 is significantly associated with PD in patients with pSjS.

## W65-3

### Anti-Ribosomal P Antibody is involved with the pathophysiology of NP-SLE with High-Levels of CSF IL-8

Hidenaga Kawasumi, Takahisa Gono, Yasushi Kawaguchi, Yasuhiro Katsumata, Masanori Hanaoka, Hisae Ichida, Akiko Tochimoto, Yuko Okamoto, Sayuri Kataoka, Hisashi Yamanaka  
Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: None

[Objectives] NP-SLE is a poor prognostic factor in SLE patients. The vascular endothelial disorders and the degradation of blood-brain barrier might be involved in the development of NP-SLE. We measured serum autoantibodies exhaustively, and evaluated the associations between serum autoantibodies and CSF cytokines in NP-SLE. [Methods] Seventy SLE patients who had been admitted to our hospital from 2001 to 2013 on active phase were enrolled. We measured serum autoantibodies (anti-PL, anti-U1-RNP, anti-Sm, anti-ribosomal P, and anti-NR2 antibodies) and CSF cytokines (IL-6, IL-8, and IFN- $\alpha$ ). [Results] Serum anti-PL, anti-U1-RNP, anti-Sm, anti-ribosomal P, and anti-NR2 antibodies were detected in 15 (21%), 25 (36%), 14 (20%), 23 (33%), and 23 (33%) patients, respectively. NP-SLE was diagnosed in 24 patients. In a multivariate analysis, anti-ribosomal P was associated with the development of NP-SLE. The CSF levels of IL-8 were significantly higher in the NP-SLE subset. High levels of CSF IL-8 (>30 pg/ml) were significantly (P<0.001) associated with the developments of NP-SLE. Anti-ribosomal P and anti-NR2 were significant autoantibody involved in the high levels of CSF IL-8. [Conclusion] Anti-Ribosomal P Antibody is involved with the pathophysiology of NP-SLE with High-Levels of CSF IL-8.

## W65-4

### **IgM anti-DNA antibodies may be protective for renal involvement in patients with SLE**

Masaaki Nakano, Hiroe Sato, Takeshi Nakatsue, Yoko Wada, Takeshi Kuroda, Ichiei Narita

Division of Nephrology and Rheumatology, Niigata University Medical and Dental Hospital, Niigata, Japan

Conflict of interest: None

[Objectives] The objective of this study is to investigate the association between patterns of anti-DNA antibody isotypes and renal involvement in patients with SLE. [Methods] IgG and IgM class anti-DNA antibodies were analysed by ELISA. [Results] The IgM/IgG ratio of anti-DNA antibodies represented a significant parameter to clarify the presence of lupus nephritis. [Conclusion] IgM anti-DNA antibodies may be protective for renal involvement in patients with SLE.

## W65-5

### **The clinical role of an antineutrophil cytoplasmic antibody (ANCA) in the systemic lupus erythematosus (SLE)**

Yuko Shirota, Tomoaki Machiyama, Kanae Akita, Yukiko Kamogawa, Kyohei Nakamura, Ryu Watanabe, Yoko Fujita, Hiroshi Fujii, Tomonori Ishii, Hideo Harigae

Department of Hematology and Rheumatology, Tohoku University Hospital, Miyagi, Japan

Conflict of interest: None

[Background] In SLE, neutrophils are activated, and dying by NETosis. PR3 and MPO were contained in the NETs, which are the cause of ANCA, also ANCA appearing in inflammation and malignancy. [Objectives] To evaluate the clinical role of ANCA in SLE [Method] 462 cases of SLE were observed from 1997 to 2014 in our hospital. Clinical symptoms were evaluated by the medical records in ANCA positive cases. I group: suspected/ certain cases of ANCA associated vasculitis (AAV) by diagnostic criteria. II group: not fulfilled the criteria although had AAV associated symptoms. ANCA and SLEDAI were analyzed by unpaired t-test. [Result] 44 cases are ANCA positive. As for I group are 11 and II group are 21, other 2 sepsis, 2 malignancy, 2 pregnant/ deliveries, 2 ulcerative colitis, and unknown in 4 cases. I group had significantly high C-ANCA levels compared to II group ( $149\pm 125$ ,  $15\pm 19$ U/ml). SLEDAI toward trend increase in I and II group ( $14\pm 7$ ,  $11\pm 6$ ), and were lower in sepsis and malignancy ( $2\pm 1.4$ ,  $0.4\pm 0.7$ ). 3 of I and 3 of II groups had nephritis. I group had active regions such as crescent formations, yet the deposition of the immune complex were not severe. [Conclusion] Monitoring a SLE activity and ANCA suggested a useful to recognize the complication of AAV, and other morbidity.

## W65-6

### **The efficacy of rituximab for refractory thrombotic microangiopathy associated with connective tissue diseases regardless of ADAMTS-13 activity levels**

Yohei Takeuchi, Tomohiro Kameda, Risa Wakiya, Hiroki Ozaki, Hiromi Shimada, Shusaku Nakashima, Miharuru Izumikawa, Kentaro Susaki, Hiroaki Dobashi

Department of Internal Medicine, Division of Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University, Kagawa, Japan

Conflict of interest: None

[Objectives] Recently, it has been described in many reports that B cell has important roles in connective tissue disease (CTD). Rituximab (RTX) is anti-CD20 monoclonal antibody that is widely known as effective for patients with several CTD. Thrombotic microangiopathy (TMA) is developed in CTD occasionally. CTD-TMA especially with normal activity of von Willebrand factor cleaving protease, ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member-13) is often resistant for plasma exchange conducted for thrombotic thrombocytopenic purpura with ADAMTS-13 inhibitor and lack of ADAMTS-13 activity as a first line treatment. We have reported in the cases

report that RTX treatment was effective for CTD-TMA which was refractory to plasma exchange. [Methods] Six patients with refractory CTD-TMA (SLE: 3, SS: 2, MCTD: 1) were investigated retrospectively. [Results] Cytopenia related to TMA was improved immediately after initial administration of RTX regardless of ADAMTS-13 activity levels. They all have sustained in remission for at least 24 weeks. RTX was well tolerated and no serious complications were reported. [Conclusion] RTX treatment can be an effective for treatment of refractory CTD-TMA regardless of ADAMTS-13 activity levels.

## W66-1

### **Prognosis and immunosuppressive treatment of exacerbated interstitial lung disease (ILD) in rheumatoid arthritis**

Mineto Ota, Yukiko Iwasaki, Hiroaki Harada, Oh Sasaki, Yasuo Nagabuchi, Shinichiro Nakachi, Shuji Sumitomo, Hirofumi Shoda, Keishi Fujio, Kazuhiko Yamamoto

Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Conflict of interest: None

[Objectives] ILD is a common comorbidity of RA. However, few evidence-based treatments exist on its exacerbation. We aimed to find out the clinical features, treatment, and prognosis of exacerbated RA-ILD cases. [Methods] We investigated 17 RA patients who required hospitalization at our department for the aggravation of ILD between 2006 and 2013. [Results] The mean age and RA duration were  $69.8\pm 9.8$  and  $5.9\pm 4.8$  years, respectively. In 7 cases, the RA diagnosis was preceded by ILD onset. All of the cases were treated with glucocorticoid (GC) equivalent to more than 20 mg of prednisolone; 5 with GC alone, 3 with TAC, 4 with CyA, and 5 with CYC  $\pm$  other concomitant drugs. When analyzing all the cases, therapeutic interventions limit the potential for exacerbation (change rate of %VC;  $-2.63\%$ / month vs  $0.50\%$ / month,  $p<0.05$ ). The respiratory function at the time of therapy initiation was poorer in CyA and CYC groups than the others. [Conclusion] Immunosuppressive therapy improved the respiratory function of aggravated RA-ILD cases. In our facility, CyA or CYC were used in severe cases, and CYC may have a better life prognosis. Moreover, the importance of B cells in pulmonary manifestations of RA is to be discussed based on the information of the PBMC analysis in a CYC-treated patient.

## W66-2

### **Predictors of mortality in patients with interstitial lung disease treated with corticosteroids**

Kiyoshi Migita<sup>1</sup>, Nozomi Iwanaga<sup>1</sup>, Yasumori Izumi<sup>1</sup>, Yoshika Shigemitsu<sup>1</sup>, Chieko Kawahara<sup>1</sup>, Eiiichi Suematsu<sup>2</sup>, Yojiro Kawabe<sup>3</sup>, Hiroshi Furukawa<sup>4</sup>, Shigeto Tohma<sup>4</sup>

<sup>1</sup>Department of Rheumatology, Nagasaki Medical Center, National Hospital Organization, Omura, Japan, <sup>2</sup>Department of Collagen Disease, Kyushu Medical Center, National Hospital Organization, Fukuoka, Japan, <sup>3</sup>Department of Rheumatology, Ureshino Medical Center, National Hospital Organization, Ureshino, Japan, <sup>4</sup>Department of Rheumatology, Sagami Hospital, National Hospital Organization, Sagami, Japan

Conflict of interest: None

[Objectives] We conducted a multicenter prospective study on 104 patients diagnosed with idiopathic interstitial pneumonias (IIPs) and 29 patients diagnosed with connective tissue disease-associated interstitial lung disease (CTD-ILD). [Methods] We compared the clinical characteristics, high-resolution computed tomography (HRCT) imaging date, and outcomes. [Results] Of 133 patients with IIPs ( $n=104$ ) or CTD-ILD ( $n=29$ ), 44 patients died during the follow-up period (mean:  $1.6\pm 0.78$  years). Patients with IIPs seemed to be associated with worse survival compared with those with CTD-ILD; however, this difference was not significant (log-rank test,  $p=0.084$ ). Significant predictors for mortality in patients with IIPs at baseline were lower for performance status and definite usual interstitial pattern (UIP) on HRCT. [Conclusion] A definite UIP pattern on HRCT and lower baseline performance status have important prognostic implications in patients with IIPs.

### W66-3

#### Clinical manifestations of Combined Pulmonary Fibrosis and Emphysema (CPFE) with Rheumatoid Arthritis

Masatoshi Kadoya, Aki Sakashita, Akiko Ido, Atsushi Omoto, Wataru Fukuda

Center for Rheumatic Disease, Japanese Red Cross Society Kyoto Dai-ichi Hospital, Kyoto, Japan

Conflict of interest: None

[Objectives] There is increasing clinical and radiologic recognition of the coexistence of emphysema and pulmonary fibrosis in the same patient, resulting in a clinical syndrome known as combined pulmonary fibrosis and emphysema (CPFE) that is characterized by dyspnea, upper-lobe emphysema, lower-lobe fibrosis. But clinical manifestations of CPFE with rheumatoid arthritis (RA) are not known. [Methods] We retrospectively investigated data from patients with RA who also have interstitial pneumonia including CPFE. The demographic characteristics of the patients, the results of pulmonary function testing, high-resolution computed tomography, and the outcomes of the patients were analyzed. [Results] Data from 53 RA patients (male 24, female 29) with Interstitial pneumonia were analyzed. 12 patients (male 11, female 1) with CPFE were included. The mean duration of RA was 8.2 years. Moderately impaired pulmonary function test results and markedly reduced carbon monoxide transfer capacity were observed. All of 12 patients were current or former smokers. These findings were different from those with UIP pattern. [Conclusion] CPFE warrants inclusion as a novel, distinct pulmonary manifestation within the spectrum of RA-associated lung diseases in smokers or former smokers.

### W66-4

#### Analysis of Rheumatoid Arthritis Patients with Organizing Pneumonia

Yukiko Tokuda<sup>1</sup>, Nobuyuki Ono<sup>1</sup>, Yukihide Ono<sup>1</sup>, Yuri Sadanaga<sup>1</sup>, Satoko Tashiro<sup>1</sup>, Rie Suematsu<sup>1</sup>, Syuichi Koarada<sup>1</sup>, Akihide Ohta<sup>2</sup>, Yoshifumi Tada<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Faculty of Medicine, Saga University, Saga, Japan, <sup>2</sup>Institute of Nursing, Faculty of Medicine, Saga University, Saga, Japan

Conflict of interest: None

[Objectives] To reveal clinical features of organizing pneumonia (OP) as lung manifestation of rheumatoid arthritis (RA). [Methods] We reviewed RA patients associated with OP since 1998 to September 2014. Prognoses were analyzed in patients whose follow-up periods were longer than 6 months. [Results] Twenty patients (8 males and 12 females) with 25 events were enrolled. The average age at onset was 56.5 years. All of them were seropositive RA patients. Eight patients had RA-associated airway disease, while 4 had interstitial lung diseases (UIP/NSIP patterns). Eight patients were ever-smokers, 5 had sinusitis, 3 had COPD, and 2 suffered from asthma. Totally, 17 patients had some pneumonia risks, such as respiratory disorders and/or smoking history. Corticosteroids were increased in 74% of the cases. We evaluated prognoses of 15 patients (19 events). There was no death during follow-up period (average 52.4 months). Four patients had relapses of OP, among them one patient showed 3 OP episodes. All recurrent cases had airway/lung disorders. At the final observations, 4 of 15 patients were steroid free. [Conclusion] It is supposed that chronic inflammation of respiratory tract plays a role in the development of RA-related OP.

### W66-5

#### Safety and efficacy of biological therapy with rheumatoid arthritis-associated pulmonary disease as interstitial lung disease or airway disease

Shogo Banno, Hironobu Nobata, Wataru Kitagawa, Hirokazu Imai  
Department of Internal Medicine, Division of Rheumatology and Nephrology, Aichi Medical University, School of Medicine, Aichi, Japan

Conflict of interest: None

[Objectives] RA associated lung disease as an extra-articular manifestation is an important risk factor of infection during the biological

treatment. [Methods] We estimated 62 RA patients divided into two groups: air-way disease group (n=24) with bronchiolitis or bronchiectasis including 8 pulmonary MAC and IP/COPD group (N=38) with 21 NSIP, 8 UIP and 9 COPD including 6 CPFE patients. [Results] Baseline DAS-CRP was high disease activity (Air-way group 5.24, IP/COPD 5.38). The adverse events were occurred and stopped biologics in 2 of air-way group (1 bacterial pneumonia, 1 exacerbated pulmonary MAC) and 10 of IP/COPD (5 PCP, 2 exacerbated IP, 1 lung cancer). All were recovered complicated infection. Four (6%) were dead after 24 months stopped biologics treatment. All were IP/COPD group patients, and 2 with CPFE were caused by pyo-pneumothorax. RA patients with 33% of airway disease and 66% of IP/COPD were treated monotherapy of biologics. The low-disease activity or clinical remission was achieved 29% with air-way group and 39% with IP/COPD group. DAS-CRP were improved in air-way and IP/COPD group to 3.09 and 2.68, respectively. [Conclusion] We thought biological treatment was safety and effective in RA patients complicated with the air way disease or IP/COPD.

### W66-6

#### Incidence rate and risk factors for tuberculosis in Japanese patients with rheumatoid arthritis during 12 years observational period in the IORRA cohort

Rei Yamaguchi, Kumi Shidara, Eiichi Tanaka, Eisuke Inoue, Yoko Shimizu, Akiko Kobayashi, Naoki Sugimoto, Daisuke Hoshi, Eri Sato, Yohei Seto, Ayako Nakajima, Shigeki Momohara, Atsuo Taniguchi, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Objectives] To examine the incidence rate and risk factors for tuberculosis (TB) in Japanese RA patients in daily practice. [Methods] Among the patients with RA enrolled in the IORRA at least two times from 2002 to 2013, all TB cases extracted based on patients' self-reporting biannually were confirmed by their medical records. Standardized incidence rate (SIR) of TB were calculated according to the incidence in general Japanese population. Risk factors for TB were examined using multiple Cox regression analysis. [Results] Among 10,415 patients with RA (male 1,823, female 8,592) with 108,175 patient-years (male 17,035, female 91,140), 23 TB cases [Average age 56.2 years; %male 32%; %steroid use 56.5% (mean 5.0 mg/day); %biologics use 21.7%] excluding cases before RA diagnosis or enrollment in the IORRA out of 35 TB confirmed cases were the cases in this study. The SIR of TB was 0.85 [95%CI 0.54-1.27]; [male 0.84 (95%CI: 0.36-1.66), female 0.85 (95%CI: 0.48-1.40)]. The risk factors for TB were male (p<0.01), older age (p<0.05), low BMI (p<0.01) and biologic use (p<0.05). [Conclusion] There was no significant difference in the incidence rate of TB in Japanese RA patients in comparison with general population. Biologics use was significant risk factor for TB.

### W67-1

#### The characteristics of malignant lymphoma developing in rheumatoid arthritis patients

Yasunobu Takizawa, Satomi Kobayashi, Keigo Setoguchi  
Department of Allergy and Immunological Diseases, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Conflict of interest: None

[Objectives] To clarify the characteristics and the risk factors of malignant lymphoma (ML) in rheumatoid arthritis (RA) patients [Methods] The medical records of RA patients with ML who had ever visited our hospital after 2005 were investigated. [Results] Of the 27 RA patients with ML (5 male, 22 female), methotrexate (MTX) was used in 20 patients for 3.6 ± 4.5 years. Biologics were used in 4, all concurrently with MTX. Pathologically, ML comprised 15 diffuse large B-cell lymphoma (11 with MTX: 4 without MTX), 5 Hodgkin's disease (5:0), 3 mucosa-associated lymphoid tissue (2:1), 2 mantle cell (1:1), 1 follicular (0:1), and 1 angioimmunoblastic T-cell lymphoma (1:0). Nine of 16 patients (8 of 13 with MTX vs. 1 of 3 without MTX) were positive for Epstein-Barr virus-related antigen. Antitumor treatment was given to 24 patients: che-

motherapy including radiation and stem cell transplant in 23 and radiation alone in 1 patient, while spontaneous regression (SR) occurred in 2 and one died before treatment. Eight patients died, six from ML and two from infection after remission of ML. [Conclusion] While MTX-related lymphoproliferative disease including ML occasionally shows SR, our data suggested that RA-related ML, regardless of MTX use, was no less severe than ML in general.

### W67-2

#### Efficacy and safety of DMARDs for patients with relapsed-rheumatoid arthritis after treatment of methotrexate-associated lymphoproliferative disorders

Shinya Hirata, Eiko Miyagawa, Komei Sakata, Ayako Fujimoto, Mikako Iwakura, Koyu Hoshino

Department of Rheumatology & Clinical Immunology, Kumamoto University Hospital, Kumamoto, Japan

Conflict of interest: None

[Objectives] Methotrexate (MTX) serves as a key drug in treating patients (pts) with RA, but certain RA pts treated with MTX develop lymphoproliferative disorders (MTX-LPD). When RA recurred after treatment of MTX-LPD, efficacy and safety of DMARDs was unclear. [Methods] We analyzed 5 pts (a male and 4 females) with recurred RA, whose MTX-LPD was treated from January 2010 to October 2013. [Results] The mean age was 66 years old, mean disease duration of RA 12 years, mean total dose of MTX 1,200 mg, and mean duration of MTX treatment 40 months. Epstein-Barr virus infection was detected in tumor tissues from 2 of 4 pts analyzed. Three pts were treated with solely withdrawal of MTX, and 2 pts were chemotherapy. RA recurred within mean 10 months after the treatment. Tacrolimus was administered to all pts, bucillamine was to 4 pts, salazosulapyridine to 2 pts, iguratimod to 2 pts, biologic DMARDs (etanercept, abatacept or golimumab) to 2 pts, and low dose prednisolone to 4 pts. Four pts achieved remission or low disease activity of RA. LPD did not recur in all pts during observation period from 13 months to 59 months. [Conclusion] DMARDs except MTX were safely used without recurrence of LPD in pts with RA recurred after treatment of MTX-LPD.

### W67-3

#### Disease relapse in Methotrexate-associated lymphoproliferative disorder (MTX-LPD): a retrospective analysis of 16 patients in our department

Koji Kobayashi, Atsumu Osada, Atsushi Ihata, Shohei Nagaoka

Department of Rheumatology, Yokohama Minami Kyousai Hospital, Yokohama, Japan

Conflict of interest: None

Objectives: It is well recognized that patients of rheumatoid arthritis with MTX develop MTX-LPD. The objective of this study is to investigate MTX-LPD cases in our department and to identify predictive factors of relapse. Methods: We evaluated the clinical characteristics, pathological and laboratory findings, treatment and course in 16 MTX-LPD cases. Results: Average age of MTX-LPD onset was 70.6 years (52~85) and average time of its onset from administration of MTX was 8.3 years (2.2~19.8). Extranodal sites were occurred in 37%(6/16). 12 cases were includes in DLBCL (n=3), HL (N=3), FL (n=1), PTCL NOS (n=1), AILD (n=1), PEL (n=1), no malignancy (n=3), three cases were not proceeded. MTX was stopped in all patients, and 3/16 (2: DLBCL, 1: PTCL-NOS) started chemotherapy. All lesions were regressed, but the relapse was observed in 25% (4/16). Relapse was associated with Sjögren's syndrome complication (p=0.04). Conclusions: All cases of MTX-LPD in our department were improved, however 25% of cases were relapsed. We must follow the patients of MTX-LPD after remission especially in high risk relapse group of Sjögren's syndrome complication.

### W67-4

#### Factor analysis of deterioration of renal function in rheumatoid arthritis (RA) patients

Ryo Inoue<sup>1</sup>, Kinya Kitada<sup>2</sup>, Yasushi Kakuchi<sup>1</sup>, Hiroshi Fujii<sup>2</sup>, Kazunori

Yamada<sup>2</sup>, Mitsuhiro Kawano<sup>2</sup>

<sup>1</sup>Division of Internal Medicine and Rheumatology, Ishikawa-ken Saiseikai Kanazawa Hospital, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School

Conflict of interest: None

[Objectives] In RA patients deterioration of renal function may be caused by the disease itself or drugs used to treat it. We assessed the background of deterioration of renal function in RA patients. [Methods] The study group consisted of 223 RA patients. We calculated eGFR using Cr (eGFR<sub>Cr</sub>), and divided the patients into two groups: group A with a deterioration ratio  $\geq 10\%$ , n=49, and group B deterioration ratio <10%, n=174. We searched for associated factors. [Results] The average age (years), body weight (kg), disease duration (years), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), immunoglobulin, urine protein, urine albumin, presence or absence of taking non-steroidal anti-inflammatory drugs, development of diabetes mellitus, hypertension, and kidney disease showed no differences between the two groups. DAS28-CRP, SDAI and CDAI of the patients in group A were 2.05, 8.89, 8.26 and while those in group B were 1.81, 7.71 and 6.51, respectively, and showed significant differences between the two groups. [Conclusion] Disease activity exerted an influence on renal function in RA patients even within one year.

### W67-5

#### The incidence of malignancies in patients with rheumatoid arthritis enrolled in the IORRA cohort during a 14-year observation period (2000 to 2013)

Naoki Sugimoto, Eiichi Tanaka, Eisuke Inoue, Rei Yamaguchi, Yoko Shimizu, Akiko Kobayashi, Kumi Shidara, Daisuke Hoshi, Ayako Nakajima, Shigeki Momohara, Atsuo Taniguchi, Hisashi Yamanaka  
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Objectives] To examine the incidence of malignancies in patients with rheumatoid arthritis (RA). [Methods] Among outpatients with RA enrolled in the IORRA cohort from 2000 to 2013, all malignancies were extracted from patients' self-reporting and confirmed by medical records. With regard to overall malignancies and malignancies at each site, standardized incidence rates (SIR) were calculated according to the data from the general Japanese population. [Results] Data from 11,106 patients with RA (1,992 males; 9,114 females), including 122,706 p-y (19,597 males; 103,109 females), were analyzed, and 830 malignancies were confirmed (676.4 malignancies/100,000 p-y, SIR 0.96, 95% CI 0.90-1.03). Malignant lymphoma and lung cancer were the most frequent types of malignancy (114 cases), and a significant increase in SIR was identified for malignant lymphoma in both males (SIR 4.62) and females (SIR 5.27) and for lung cancer in males (SIR 1.36) with RA. [Conclusion] Although no significant difference in the overall incidence of malignancies in RA patients was noted compared with the general population, there was a significant difference in the sites of malignancies and a significant increase in the incidence of malignant lymphoma and lung cancer in males with RA.

### W67-6

#### Cross-sectional analysis about the HBV-related antibodies in the patients with rheumatoid arthritis: First report of a multicenter, prospective, observational study for reactivation of hepatitis B virus with the immunosuppressive therapy for rheumatic diseases by the fifteen hospitals founded by Japanese Red Cross

Wataru Fukuda<sup>1</sup>, Tadamasa Hanyu<sup>2</sup>, Munetoshi Nakashima<sup>3</sup>, Shinichi Mizuki<sup>4</sup>, Masaki Katayama<sup>5</sup>, Toshihisa Kanamono<sup>6</sup>, Masayuki Miyata<sup>7</sup>, Yuichi Handa<sup>8</sup>, Yoshinobu Koyama<sup>9</sup>, Hiroyuki Hagiya<sup>10</sup>, Kaoru Arii<sup>11</sup>, Toshiyuki Kitaori<sup>12</sup>, Yoshinori Urushidani<sup>13</sup>, Takahito Yamazaki<sup>14</sup>, Atsushi Omoto<sup>1</sup>, Shigeko Inokuma<sup>15</sup>

<sup>1</sup>Center for Rheumatic Disease, Japanese Red Cross Kyoto Daiichi Hospital, <sup>2</sup>Department of Rheumatology, Nagaoka Red Cross Hospital, <sup>3</sup>Department of Rheumatology, Japanese Red Cross Nagasaki Genbaku Hospital, <sup>4</sup>Department of Rheumatology, Matsuyama Red Cross Hospital,

<sup>5</sup>Department of Rheumatology, Osaka Red Cross Hospital, Osaka, <sup>6</sup>Department of Orthopedics, Nagano Red Cross Hospital, <sup>7</sup>Department of Internal Medicine, Fukushima Red Cross Hospital, <sup>8</sup>Department of Rheumatology, Saitama Red Cross Hospital, <sup>9</sup>Department of Rheumatology, Okayama Red Cross Hospital, <sup>10</sup>Department of Rheumatology, Yokohama-City Bay Red Cross Hospital, <sup>11</sup>Department of Internal Medicine, Japanese Red Cross Kochi Hospital, <sup>12</sup>Department of Orthopedics, Fukui Red Cross Hospital, <sup>13</sup>Department of Rheumatology, Matsue Red Cross Hospital, <sup>14</sup>Department of Rehabilitation, Japanese Red Cross Society Kyoto Daini Hospital, <sup>15</sup>Department of Allergy and Rheumatic Diseases, Japanese Red Cross Medical Center

Conflict of interest: None

[Objectives] To investigate the prevalence of reactivation of hepatitis B virus (HBV) with the immunosuppressive therapy for the patients with rheumatic diseases, we started multicenter, observational, prospective study by fifteen hospitals founded by Japanese Red Cross. [Methods] Patients with immunosuppressive therapy for rheumatic disease showing negative HBs antigen and positive anti-HBs or anti-HBc antibody were registered. HBV DNA quantitation, disease activity and immunological indices and treatment are monitoring regularly. We present the cross-sectional analysis about the HBV-related antibodies as a first report. [Results] In 976 registered RA patients, patients with positive anti-HBc and negative anti-HBs (11.9%) shows no significant differences about immunological indices and the treatment compared to ones with both positive (70.5%). 272 patients used biologics did not show any differences in hepatic function, disease activity, titers of anti-HBs and anti-HBc compared to other patients. [Conclusion] It is speculated that patients with negative anti-HBs and the patients using biologics might be higher risk for reactivation of HBV, but we didn't recognize any characteristics suggesting the beginning of reactivation of HBV in those groups of patients.

## W68-1

**Serum CD146 levels as a biomarker of patients with Behçet's disease**  
Sayuri Okuda<sup>1</sup>, Tomoko Ito<sup>2</sup>, Naoto Tamura<sup>2</sup>, Kurisu Tada<sup>2</sup>, Ken Yamaji<sup>2</sup>, Yoshinari Takasaki<sup>2</sup>, Kazunori Kato<sup>1</sup>

<sup>1</sup>Department of Biomedical Engineering, Toyo University, Saitama, Japan, <sup>2</sup>Department of Internal Medicine and Rheumatology, Juntendo University, Tokyo, Japan

Conflict of interest: None

[Objectives] Interleukin 17-producing Th17 cells are associated with certain inflammatory autoimmune diseases. Previous reports indicated that MCAM (melanoma cell adhesion molecule; CD146) is expressed on Th17 cells that are significantly elevated in Behçet's disease (BD). We recently established sandwich ELISA for soluble CD146 (sCD146). The aim of this study is to determine the levels of sCD146 in the serum of patients with BD, and to examine the relationship between the levels of sCD146 and the clinical variables as a biomarker of BD. [Methods] Blood samples were drawn from patients fulfilling criteria for BD. Levels of sCD146 were quantified in 20 serum samples from patients with BD by ELISA and compared with those of 23 healthy subjects. The titers of CRP for each BD patient were determined simultaneously. [Results] Levels of sCD146 were significantly higher in patients with BD (12.1 ng/ml) than in the healthy subjects (7.9 ng/ml;  $p < 0.01$ ). However, no correlation between sCD146 and CRP value was observed. [Conclusion] We identified the presence of sCD146 in BD serum. Correlation between sCD146 and the clinical variables such as uveitis, erythema nodosum and ulcerative diseases will be determined.

## W68-2

**Implication of infliximab trough level and anti-infliximab antibody in efficacy and safety issue in patients with Behçet's disease**

Mitsuhiro Takeno<sup>1</sup>, Yohei Kirino<sup>2</sup>, Hiroto Kikuchi<sup>3</sup>, Kazuyoshi Saito<sup>4</sup>, Masataka Kuwana<sup>5</sup>, Shunsei Hirohata<sup>6</sup>, Yoshiaki Ishigatsubo<sup>2</sup>

<sup>1</sup>Clinical Laboratory Department, Yokohama City University Graduate School of Medicine, <sup>2</sup>Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, <sup>3</sup>Department of Internal Medicine, Teikyo University Graduate School of Medicine, <sup>4</sup>The First Department of Internal Medicine, University of Oc-

cupational and Environmental Health, <sup>5</sup>Department of Allergy and Rheumatic Diseases, Nippon Medical School, <sup>6</sup>Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Japan

Conflict of interest: None

[Objectives] To investigate effects of infliximab (IFX) trough levels and antibody toward IFX (ATI) on efficacy and adverse events in Behçet's disease (BD) patients receiving IFX. [Methods] IFX trough level and ATI were determined by ELISA in sera from 152 BD patients receiving IFX and 8 patients who discontinued it. Therapeutic response was determined by physicians' assessment. [Results] IFX trough level was  $5.1 \pm 6.1$  mg/ml at  $7.6 \pm 1.0$  wk after the last infusion. The level was significantly lower in active phase than in inactive ( $3.0 \pm 6.0$  µg/ml,  $5.2 \pm 5.1$  µg/ml,  $p < 0.05$ ). ROC analysis determined the cut-off was 0.67 µg/ml. In physicians' assessment, unfavorable clinical response was associated with low IFX trough level and positive ATI. ATI was detected in 18 patients (11.3%) including 5 of 8 patients who discontinued IFX. Infusion reaction (IR) was more frequent in ATI positive patients (81%) than negative ones (3%,  $p < 0.05$ ). Shortening infusion intervals restored IFX level and clinical efficacy in 2 patients, whereas switching to another TNF inhibitor was successful in 2 patients having serious IR. [Conclusion] Efficacy of IFX depends on the trough level. Shortening the infusion interval and switching to another TNF inhibitor can be optional when efficacy of IFX is reduced.

## W68-3

**Adalimumab was useful for parastomal pyoderma gangrenosum in a patient with intestinal Behçet disease**

Shinya Hirahara, Makiko Kimura, Masako Inagaki, Manabu Tanabe, Takashi Ogasawara, Mutsuto Tateishi  
Tokyo Metropolitan Ohtsuka Hospital, Tokyo, Japan

Conflict of interest: None

[Case] 48 years old female was diagnosed as intestinal Behçet's disease at the age of 41. She has been treated with prednisolone, colchicine and Infliximab. She had intestinal perforation in November 2013 and had colostomy. Since then Infliximab was withdrew. Parastomal ulcer began to appear around stoma area since January 2014, which was relieved with rest but exacerbated repeatedly. In August she was admitted because of exacerbation of the ulcer accompanied with fever and joint pain. Biopsy of the granulation tissue was revealed neutrophil infiltration suggesting the diagnosis of pyoderma gangrenosum merger. She was intolerated with high dose prednisolone. We started Adalimumab 40mg every other week. Fever and joint pain was disappeared soon. One week later necrotic tissue around the stoma was felt off and improved. [Clinical significance] Pyoderma gangrenosum was known as complication of inflammatory bowel disease. Most of the past reports were the cases of ulcerative colitis and Crohn's disease, however, the case of Behçet's disease is quite rare. As far as we know this is the first report of Behçet's disease complicated with parastomal pyoderma gangrenosum and treated successfully with Adalimumab.

## W68-4

**Atrophy of Hippocampal Region in Chronic Progressive Neuro-Behçet's Disease**

Hiroto Kikuchi<sup>1</sup>, Kurumi Asako<sup>1</sup>, Maki Takayama<sup>1</sup>, Daisuke Tsukui<sup>1</sup>, Mai Okubo<sup>1</sup>, Akiko Okamoto<sup>1</sup>, Yoshitaka Kimura<sup>1,3</sup>, Toshihiro Nanki<sup>1,2</sup>, Hajime Kono<sup>1</sup>, Shunsei Hirohata<sup>4</sup>

<sup>1</sup>Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan, <sup>2</sup>Teikyo Academic Research Center, Teikyo University School of Medicine, Tokyo, Japan, <sup>3</sup>Department of Allergy and Rheumatology, The University of Tokyo, Japan, <sup>4</sup>Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan

Conflict of interest: None

[Objectives] We examined the volumes of hippocampus in order to determine the responsible lesions for neurobehavioral changes in chronic progressive neuro-Behçet's disease (CPNB). [Methods] 13 patients with

CPNB (11 males and 2 females, age  $51.2 \pm 12.1$ ) and 13 patients with Behçet's disease without NB (non-NB) (10 males and 3 females, age  $54.4 \pm 11.4$ ) were studied. Severity of gray matter loss in the hippocampal region and whole brain were investigated by the software for VSRAD, calculating the indicators of the degrees of hippocampal region atrophy (HAI) and those of whole-brain atrophy (WBAI). The areas of brainstem were measured on mid-sagittal sections of T1-weighted images of brain MRI using image analysis software Image J. [Results] The VSRAD analysis showed that HAI was significantly increased in CPNB compared with in non-NB. Although less markedly, WBAI was significantly higher in CPNB than in non-NB. Neither HAI nor WBAI was correlated with age. Whereas all the patients with CPNB showed brainstem atrophy, there was no significant correlation between HAI and the rate of brainstem atrophy. [Conclusion] These results indicate that hippocampus, in addition to brainstem, is a commonly affected lesion in CPNB, accounting for progressive neurobehavioral changes.

## W68-5

### Two rebellant cases of intestinal Behçet's disease related myelodysplastic syndrome with trisomy 8

Nobuyasu Ishii<sup>1</sup>, Yoshio Ozaki<sup>1,2</sup>, Toshiharu Sasaki<sup>1,2</sup>, Minoru Shigesaka<sup>1</sup>, Saki Tsujimoto<sup>1,2</sup>, Akihiro Tanaka<sup>1,2</sup>, Keiko Shimamoto<sup>1,2</sup>, Tohru Nishizawa<sup>1</sup>, Hideki Amuro<sup>1</sup>, Yonsu Son<sup>1,2</sup>, Shosaku Nomura<sup>1</sup>

<sup>1</sup>First Department of Internal Medicine, Kansai Medical University, Hirakata City, Japan, <sup>2</sup>Department of Rheumatology and Clinical Immunology, Kansai Medical University Hirakata Hospital, Hirakata City, Japan

Conflict of interest: None

[Objectives] Here, we report two rebellant cases of intestinal Behçet's disease related myelodysplastic syndrome with trisomy 8. [Case 1] 37 year-old man had suffered with continual oral ulcers, and he was pointed out leukocytopenia and CRP elevation. Examination of colonofiberscope showed large ulcer on his ileocecum. Moreover trisomy 8 (20/20) in chromosomal composition from bone marrow biopsy was indicated. We diagnosed him as intestinal BD related MDS and treatment with PSL include pulse therapy. Treatment with immunosuppressants and biologic agents such as IFX had limited benefit in this patient. He had a brief response to treatment with PSL of 20mg or more, and Colectomy was necessary for his treatment. [Case 2] 54 year-old man complained abdominal pain and oral ulcers. His WBC was decreased and CRP was elevated. After treatment with ADA, he was referred to our hospital. He had trisomy 8 (16/20) in chromosomal composition, and typical ileocecum ulcer too. Immunosuppression consisting of high-dose steroid and biological agent (ADA, IFX, TCZ, ABT, GLM) was given. However only 25mg or more PSL could curb inflammation. [Conclusion] Intestinal BD related MDS with trisomy 8 is regarded as a "peculiar" subtype of BD. Some cases have poor treatment reactivity.

## W68-6

### A case of intestinal Behçet's disease complicated with myelodysplastic syndrome with trisomy 8 required the ileocecal resection

Kei Fujioka, Daisuke Murakami, Koichiro Taguchi, Tatsuo Ishizuka  
Center of General Internal Medicine and Rheumatology, Gifu Municipal Hospital, Gifu, Japan

Conflict of interest: None

A 46-year-old man was hospitalized with pancytopenia and bloody stool, and diagnosed as myelodysplastic syndrome showing a chromosomal abnormality (trisomy 8 positivity). Colonoscopic examination revealed an ileocecal ulcer. He was diagnosed as the intestinal Behçet's disease from aphthous ulcer, folliculitis, and positive needle reaction, one years ago. He became re-hospitalization on April 3. Treatment with PSL and mesalazine was started, but his symptoms were not improved in spite of additional azathioprine treatment. Therefore, adalimumab and infliximab treatment were done, but their effects were temporary. Colonoscopic examination revealed an ileocecal ulcer perforation with internal fistula. Ileocecal resection was performed on April 30. Six ulcers were observed in the ileum. After the operation and abdominal symptoms disappear and the activity is suppressed with PSL 5 mg/day. The intestinal Behçet's disease with myelodysplastic syndrome have known as an intractable case,

and the most of those have 8 trisomy positivity. Serum TNF $\alpha$  and IL-6 levels were decreased after operation, and cytokine production from an excision portion has been suspected. These results suggest that even if a bone marrow transplantation might be difficult, the ileocecal resection should be considered.

## W69-1

### Rebamipide, an amino acid analog of 2(1H)-quinolinone, inhibits formation of human osteoclasts

Yuki Nanke, Tsuyoshi Kobashigawa, Toru Yago, Manabu Kawamoto, Hisashi Yamanaka, Shigeru Kotake

Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: None

[Objectives] Drug repositioning (DR) has been growing in importance recently. DR has a significant advantage over traditional drug development because the repositioned drug has already passed toxicity; its safety is known; and the risk of adverse toxicology are reduced. In the current study, we investigated the role of rebamipide, a mucosal protective agent, on human osteoclastogenesis. [Methods] Peripheral blood mononuclear cells (PBMCs) were cultured in the presence of M-CSF and sRANKL. Osteoclast formation was evaluated by immunohistological staining for CD51/61 (vitronectin receptors). Osteoclast formation, in the presence or absence of rebamipide (0, 1, 3 mM), was observed by time lapse and actin ring formation. Number of absorption and area of absorption were calculated by osteologic plates. Pit formation was studied by 3D SEM. [Results] Rebamipide inhibited the human osteoclasts formation at 3mM, a pharmacological concentration, and inhibited resorbing activity dose-dependently. Rebamipide induced degradation of actin rings in mature osteoclasts. [Conclusion] These findings suggest rebamipide would be useful for osteoporosis and rheumatoid arthritis.

## W69-2

### Surveillance for the use of mycophenolate mofetil (MMF) in adult patients with lupus nephritis

Shinsuke Yasuda<sup>1</sup>, Tatsuya Atsumi<sup>1</sup>, Sanae Shimamura<sup>1</sup>, Keiju Hiromura<sup>2</sup>, Ken-ei Sada<sup>3</sup>, Masaaki Mori<sup>4</sup>, Syuji Takei<sup>5</sup>, Yasushi Kawaguchi<sup>6</sup>, Naoto Tamura<sup>7</sup>, Yoshinari Takasaki<sup>7</sup>

<sup>1</sup>Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, <sup>2</sup>Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine, <sup>3</sup>Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, <sup>4</sup>Department of Pediatrics, Yokohama City University Medical Center, <sup>5</sup>Kagoshima University Hospital, Children's Medical Center, <sup>6</sup>Institute of Rheumatology, Tokyo Women's Medical University, <sup>7</sup>Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine

Conflict of interest: Yes

[Objectives] Mycophenolate mofetil (MMF) is one of the standard induction/maintenance therapies for lupus nephritis (LN) in many of the developed countries. In Japan, however, the use of MMF has not been approved for treating LN, resulting in off-label use of this immunosuppressant. In order to confirm the necessity of MMF as a treatment for LN, we surveyed retrospectively the use of MMF in Japan. [Methods] Adult patients with LN who visited enrolled hospitals from Oct 2008 to Sep 2013 were surveyed retrospectively for the initial, maximum and maintenance dose of MMF, for the safety and for the efficacy evaluated by urine protein, complement levels and anti-DNA antibody. [Results] One hundred and thirty-one LN patients including 111 females were enrolled. The average initial dose, the maximum dose and the maintenance dose of MMF was  $0.97 \pm 0.41$  g/day,  $1.57 \pm 0.60$  g/day and 1.38 g/day, respectively. Fifty-three adverse events were reported during the follow-up period. Urine protein decreased from 4.57 g/gCr to 1.16g/gCr, C3 level decreased 65.3 mg/dl to 80.0 mg/dl and anti-DNA antibody titer decreased from 292.4 IU/ml to 28.3 IU/ml. [Conclusion] The use of MMF in adult patients with LN was surveyed in Japan.

### W69-3

#### Usefulness of mycophenolate mofetil (MMF) in childhood-onset SLE~Analysis from the survey results in Japan~

Masaaki Mori<sup>1</sup>, Ryoki Hara<sup>1</sup>, Ken-ichi Nishimura<sup>1</sup>, Tomo Nozawa<sup>1</sup>, Masako Kikuchi<sup>1</sup>, Shinsuke Yasuda<sup>2</sup>, Tatsuya Atsumi<sup>2</sup>, Sanae Shimamura<sup>2</sup>, Keiju Hiromura<sup>3</sup>, Ken-ei Sada<sup>4</sup>, Syuji Takei<sup>5</sup>, Yasushi Kawaguchi<sup>6</sup>, Naoto Tamura<sup>7</sup>, Yoshinari Takasaki<sup>7</sup>

<sup>1</sup>Department of Pediatrics, Yokohama City University School of Medicine, <sup>2</sup>Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, <sup>3</sup>Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine, <sup>4</sup>Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, <sup>5</sup>Department of Pediatrics, Kagoshima University Graduate School of Medical and Dental Sciences, <sup>6</sup>Institute of Rheumatology, Tokyo Women's Medical University, <sup>7</sup>Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine

Conflict of interest: Yes

[Background] For approval of mycophenolate mofetil (MMF) in lupus nephritis (LN), the Japanese investigation was performed in "sub-committee on MMF survey in LN" of Japanese College of Rheumatology. [Methods] We report the appropriate usage and dose, safety and effectiveness of MMF in childhood-onset LN. The child case was defined as the case that MMF had begun to be given under 16 years old. This study was performed in 12 facilities, and 113 cases (89 girls, 24 boys) were enrolled. [Results] The onset age of SLE was 10.1 years (1-15 years) and the MMF-starting age was 11.8 (2.25-15). The average initial dose, the maximum dose and the maintenance dose of MMF was  $0.65 \pm 0.25$  g/day,  $1.41 \pm 0.43$  and  $1.37 \pm 0.44$ , respectively, so the doses were similar to those in Europe and U.S.A. Twenty-four adverse events were reported including herpes zoster or abdominal symptoms, but only 5 cases reduced the MMF dose and none stopped it. And, complement C3, C4 level and the anti ds-DNA antibody titer were remarkably improved, and the dose of oral glucocorticoid was decreased. [Conclusion] According to the analysis with 113 child cases, the dose of the MMF never differed from that in the previous reports, and there were no problem with the effectiveness or the safety.

### W69-4

#### 64-Week Results of a Phase 2b Dose-Ranging Study of Baricitinib, an oral JAK1/JAK2 inhibitor, in Japanese Patients with Rheumatoid Arthritis on Background Methotrexate Therapy

Yoshiya Tanaka<sup>1</sup>, Kahaku Emoto<sup>2</sup>, Douglas Schlichting<sup>2</sup>, Zhihong Cai<sup>3</sup>, Terence Rooney<sup>2</sup>, William Macias<sup>2</sup>

<sup>1</sup>The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, <sup>2</sup>Eli Lilly & Company, Indianapolis, USA, <sup>3</sup>Japan Eli Lilly K.K.

Conflict of interest: Yes

[Objectives] Baricitinib (Bari; oral JAK1/JAK2 inhibitor) was evaluated in a Phase 2b study in Japanese rheumatoid arthritis (RA) patients (pts) who had an inadequate response to methotrexate (MTX). [Methods] Part A; 145 pts were randomized to placebo (PBO), 1, 2, 4 or 8mg Bari QD (2:1:1:1:1 ratio) for 12 weeks (wks). Pts completing Part A entered Part B (52 wks duration; n=142); 4 and 8mg pts continued same dose and PBO, 1 and 2mg pts were re-randomized to 4 or 8mg. The primary objective of Part A assessed ACR20 response for combined 4 and 8mg (Bari 4+8mg) versus PBO. [Results] At Wk 12, ACR20 response rate was 77% for Bari 4+8mg and 31% for PBO ( $p \leq 0.001$ ). Adverse event (AE) rates in PBO and Bari 4+8mg were 53% and 55%, respectively. At Wk 64, ACR20 response rates were 85% and 94%(observed) and 66% and 73%(non-responder imputation (NRI)) for 4 and 8mg doses, respectively. DAS-CRP remission was similar between 4 and 8mg doses ( $>70\%$  and  $>66\%$  for observed and LOCF). Rates of AEs leading to discontinuation were 21% and 17%, rates of serious AEs were 11% and 17%, and rates of severe infection were 3% and 6% for 4 and 8mg doses, respectively. No death occurred in Part A or B. [Conclusion] Efficacy with acceptable safety was observed for Bari in combination with MTX in Japanese RA pts.

### W69-5

#### Safety and tolerability of intravenous or subcutaneous sifalimumab in Japanese patients with systemic lupus erythematosus (SLE): Interim report of a Phase II, multicenter, open-label, dosage-increase study

Tsutomu Takeuchi<sup>1</sup>, Yoshiya Tanaka<sup>2</sup>, Warren Greth<sup>2</sup>, Liangwei Wang<sup>3</sup>, M. Alex Michaels<sup>3</sup>

<sup>1</sup>Division of Rheumatology, Keio University Hospital, Tokyo, Japan, <sup>2</sup>First Department of Internal Medicine, University of Occupational and Environmental Health, Fukuoka, Japan, <sup>3</sup>MedImmune LLC, Gaithersburg, USA

Conflict of interest: Yes

[Objectives] Sifalimumab (MEDI-545) is a fully human, anti-IFN- $\alpha$  monoclonal antibody that binds to and neutralizes most IFN- $\alpha$  subtypes. As type I IFN may play a key role in SLE, the safety and tolerability of intravenous (IV) and subcutaneous (SC) sifalimumab were examined in Japanese patients (NCT01031836). [Methods] Adult patients with moderate to severe SLE received single sifalimumab 1.0, 3.0, or 10.0 mg/kg IV or 100 mg SC on Days 1 and 29, then the same dosages every 2 weeks for 24 weeks. Patients were observed for an additional 24 weeks. Additional cohorts received 600 and 1,200 mg IV dosages once every 4 weeks during the same period. There were 5 patients in each of the 6 cohorts. Primary objectives were safety and tolerability. [Results] Adverse events (AEs) occurred in 29 patients, with drug-related AEs in 25. Serious AEs occurred in 8 patients, but there were no deaths. The most common AE was nasopharyngitis, but dosage dependency was not apparent.  $C_{max}$  and AUC increased in a dosage-dependent manner in the IV cohorts. One patient in the 1,200 mg IV cohort tested positive for anti-sifalimumab antibodies, but there was no effect on PK and PD. [Conclusion] Both IV and SC dosages of sifalimumab were well-tolerated in adult Japanese patients with SLE.

### W69-6

#### Safety and tolerability of anifrolumab in Japanese patients with systemic lupus erythematosus (SLE): Interim report of a Phase II, multicenter, open-label, dosage-increase study

Yoshiya Tanaka<sup>1</sup>, Tsutomu Takeuchi<sup>2</sup>, Gabor Illei<sup>3</sup>, Liangwei Wang<sup>3</sup>, Robert Miday<sup>3</sup>

<sup>1</sup>First Department of Internal Medicine, University of Occupational and Environmental Health, Fukuoka, Japan, <sup>2</sup>Division of Rheumatology, Keio University Hospital, Tokyo, Japan, <sup>3</sup>MedImmune LLC, Gaithersburg, USA

Conflict of interest: None

[Objectives] Anifrolumab (MEDI-546) is a fully human monoclonal antibody that inhibits binding of type I IFN to IFN $\alpha$ 1 receptor. As type I IFN may play a key role in SLE, the safety and tolerability of intravenous (IV) anifrolumab were examined in adult Japanese SLE patients (NCT01559090). [Methods] Seventeen adults with moderate to severe SLE received single IV doses of anifrolumab on Days 1 and 29, then dosage every 4 weeks until Day 337. The starting dosage was 100mg Q4W, which could be increased to 300mg Q4W after Week 20 in Cohort 1 (n=6), 300mg Q4W in Cohort 2 (n=5) and 1,000mg Q4W in Cohort 3 (n=6). Primary objectives were safety and tolerability. Evaluation continued up to Day 169. [Results] Adverse events (AEs) occurred in all patients, with drug-related AEs in 12. Serious AEs occurred in 6 patients, and there were no deaths. The most common AE was nasopharyngitis, with no dosage dependency. Serum concentrations increased in a dosage-proportional manner. Trough concentrations in Cohorts 2 and 3 reached steady state by Day 85. IFN gene expression was suppressed at high dosages and high-trough concentrations. Four patients tested positive for anti-anifrolumab antibodies, with no effect on PK and PD. [Conclusion] Anifrolumab was well-tolerated in adult Japanese patients with SLE.

### W70-1

#### Evaluation of the efficacy and safety of a new JAK inhibitor ASP015K monotherapy for 12 weeks in Japanese patients with rheumatoid arthritis

Yoshiya Tanaka<sup>1</sup>, Tsutomu Takeuchi<sup>2</sup>, Satoshi Saeki<sup>3</sup>

<sup>1</sup>The First Department of Internal Medicine, School of Medicine, Univer-



sity of Occupational and Environmental Health, Kitakyushu, Japan, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan, <sup>3</sup>Global Development-Japan, Astellas Pharma Inc.

Conflict of interest: Yes

[Objectives] To evaluate the efficacy, safety and dose response of ASP015K monotherapy in Japanese patients with moderate to severe RA [Methods] In a 12-week, double-blind study, patients with active RA not on concomitant DMARD therapy were randomized equally to once daily ASP015K 25mg, 50mg, 100mg, 150mg or placebo (PBO). The LOCF was used as an imputation method for primary analysis. [Results] ASP015K 50mg, 100mg and 150mg each showed a statistically significantly higher ACR20-CRP response at week 12 in the primary endpoint as compared to PBO and the response rates increased up to 150mg. The main reason of the discontinuation was due to lack of efficacy and the rate in PBO (16.1%) was much higher than that in 150mg (1.7%). The number of patients with discontinuation due to adverse events (AEs) was comparable among the groups. The incidence of AEs was also similar between PBO and ASP015K groups. A total of 7 patients with serious AEs were observed, but there were no cases with serious infection and malignancy. [Conclusion] In Japanese patients, treatment with ASP015K as monotherapy for 12 weeks is well tolerated and efficacious. Based on the outcome, the phase3 studies are on-going in Japan.

### W70-2

#### Personalized medicine of RA using salazosulfapyridine based on Pharmacogenetics (PGx)

Ryosuke Umeda<sup>1</sup>, Goh Tsuji<sup>1</sup>, Kyosuke Abe<sup>1</sup>, Mayuko Izumi<sup>1</sup>, Ai Muta<sup>1</sup>, Yoshihide Ichise<sup>1</sup>, Yuko Uemura<sup>2</sup>, Shunichi Kumagai<sup>1,2</sup>

<sup>1</sup>Center for Rheumatic Disease, Shinko Hospital, Hyogo, Japan, <sup>2</sup>Institute of Medicine Research, Shinko Hospital, Hyogo, Japan

Conflict of interest: None

[Background] SASP is broken down into sulfapyridine (SP) and 5-ASA by bacteria in the intestine. Absorbed SP is effective on RA, and excreted from kidney after metabolized by *N-acetyltransferase2* (*NAT2*). A part of absorbed SASP is excreted into the inside of intestine by *ATP-binding cassette transporter G2* (*ABCG2*). There are reports concerning the relationship of efficacy and/or adverse effects (AEs) of SASP to polymorphisms of these genes. [Objectives] To Investigate the relationship between *NAT2* genotypes and efficacy/AEs of SASP. [Methods] Based on genotypes of *NAT2*, we classified 169 RA patients into fast (FA), intermediate (IA), and slow acetylator (SA). 1) 102 RA patients were retrospectively examined for AEs. 2) Efficacy was prospectively examined in 43 RA patients. [Results] 1) A significant difference of hepatic, hematological, and dermatological AEs was found between FA+IA and SA of *NAT2* genotype. 2) A extent of decrease in DAS28 was significantly greater in IA than FA. [Conclusion] We can provide tailor-made medicine for RA patients through the appropriate usage of SASP based on PGx. We are now checking *NAT2* genotypes before starting SASP, and changing the dosage of SASP (500-2000mg). We will also report whether *ABCG2* genotypes are related to efficacy or AEs of SASP.

### W70-3

#### Clinical and pathological characteristics of methotrexate related lymphoproliferative disorder in six patients with rheumatoid arthritis

Ai Muta, Goh Tsuji, Kyosuke Abe, Mayuko Izumi, Ryosuke Umeda, Yoshihide Ichise, Shunichi Kumagai

Center for Rheumatic Disease, Shinko Hospital, Hyogo, Japan

Conflict of interest: None

[Objectives] To investigate the clinical and histological characteristics of patients with rheumatoid arthritis (RA) who diagnosed as methotrexate-associated lymphoproliferative disorder (MTX-LPD). [Methods] We analyzed retrospectively six RA patients with MTX-LPD between 2010 and 2014 about their clinical course, histological typing, coexistence of Epstein-Barr virus (EBV) infection and prognosis. [Results] At the time of LPD diagnosis, the mean age was 70.67 years. Three were

male. Five of six cases were extranodal lymphoma. Four cases were diffuse large B cell lymphomas (DLBCL). One was polymorphic lymphoproliferative disorder (p-LPD). EBV-encoded small RNA in situ hybridization (EBER-ISH) was positive in four cases. MTX was withdrawn in all cases. Two of EBER-ISH positive cases, one was DLBCL and the other was p-LPD, obtained complete remission without chemotherapy. Other two patients with EBV could get reduction of mass, nevertheless needed rituximab due to control of RA later. [Conclusion] EBV infection was usually concerned with MTX-LPD in RA patients. Extranodal lymphoma and histological DLBCL were frequent of our cases. MTX withdrawal was effective therapy in most of cases.

### W70-4

#### Outcome of RA patients detected malignancy by screening examination before starting biologic DMARDs from data of 1736 patients with RA at University of Occupational and Environmental Health-

Hiroko Miyata, Kazuhisa Nakano, Shingo Nakayamada, Shunsuke Fukuyo, Satoshi Kubo, Ippei Miyagawa, Shintaro Hirata, Kazuyoshi Saito, Yoshiya Tanaka

The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

Conflict of interest: None

[Objectives] To clarify the outcome of RA patients (pts) complicated with cancer. [Methods] 1736 RA pts were screened using CT scan before starting biologics in our hospital between April 2005 to March 2014. We assessed the outcome of RA pts who were found to have cancer. [Results] In the wake of CT scan, cancer was diagnosed in 11 pts (lung cancer; 8, uterine cancer; 1, malignant lymphoma (ML); 1, IPMN; 1), and 10 pts out of 11 have been followed up. Although 2 pts diagnosed as advanced cancer (uterine cancer; 1, squamous cell carcinoma) were controlled in LDA or MDA with NSAIDs and low-dose corticosteroid after discontinuation of all csDMARDs, a pt with squamous cell carcinoma died 3 years after diagnosed. A pt with ML treated with chemotherapy including Rituximab was still alive and had been kept RA in remission. 6 pts with early lung cancer underwent curative surgery. 3 of them were treated with biologics, the others were treated with MTX. ETN was started in a pt with IPMN. All 7 pts had been kept RA in LDA without recurrence of cancer. [Conclusion] Screening CT before starting biologics was useful for early detection and rapid cure of lung cancer. After curative surgery, pts could be treated with MTX and/or biologics and be kept RA in LDA without recurrence.

### W70-5

#### Use of csDMARD except MTX in NinJa 2013

Toshihiro Matsui<sup>1</sup>, Atsushi Kaneko<sup>2</sup>, Jinju Nishino<sup>3</sup>, Shigeto Tohma<sup>4</sup>

<sup>1</sup>Department of Rheumatology, Sagamihara National Hospital, National Hospital Organization, <sup>2</sup>Department of Orthopaedic Surgery and Rheumatology, Nagoya Medical Center, National Hospital Organization, <sup>3</sup>Department of Orthopaedic Surgery, The University of Tokyo Hospital, <sup>4</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, National Hospital Organization

Conflict of interest: Yes

[Objectives/Methods] To analyze the use of csDMARD except MTX using the data of 13945 patients with rheumatoid arthritis (RA) registered in NinJa2013. [Results] The rate of RA patients using csDMARD except MTX were 46.6%, which has been stable for the last 5 years. The use rate of each csDMARD was as follows; SASP38.3%, BUC26.2%, TAC 22.2%, MIZ4.1%, IGR2.6%, GST2.3%, LEF2.0%, and others2.3%. Contrary to MTX, the use rate of csDMARD except MTX increased by age (29.4% in 40s→46.1% in 70s, 54.1% in ≥80y). csDMARD except MTX was used as monotherapy (group-A) in 47.2%, in combination with MTX (group-B) in 39.6%, with biologics (group-C) in 6.8%, and with MTX plus biologics (group-D) in 6.4%. The rate of group-A increased by age (10.3% in 40s→23.7% in 70s, 34.8% in ≥80y). In group-C, the use rate of biologics was ETN34.3%, TCZ32.7%, ABT19.2%, GLM6.9%, ADA 3.3%, CZP3.0%, whose trend was apparently different from in patients using MTX (ETN33.3%, IFX20.5%, TCZ14.8%, ADA12.4%, ABT9.3%,

GLM7.8%, CZP1.9%). Group-A, whose CDAI (8.0) was similar with that of group-B (7.8) but lower than that of group-C (9.0) and group-D (9.3), showed the highest average age and the lowest positive rate of RF and anti-CCP Ab. [Conclusion] csDMARD except MTX still had an important role in RA therapy.

## W70-6

### Clinical factors related to non-use of MTX in patients with rheumatoid arthritis

Shinji Motojima, Tamao Nakashita, Akira Jibatake, Kotaro Matsumoto, Akira Yoshida, Yuto Hamada

Kameda Medical Center, Rheumatology and Allergy, Kamogawa, Japan

Conflict of interest: None

The first choice of drug for RA is MTX, however, MTX is not used in some patients. We tried to extract the factors that relate to non-use of MTX retrospectively. Subjects were 420 patients with RA, with the mean age of 65.8 years (range, 20 – 98). The mean duration of illness was 13.8 years (range, 2 – 63 years). The severity of ILD was classified into 4 grades mostly by chest CT images. The numbers of MTX users and non-users were 268 and 152, respectively, with the mean dose of 8.4 mg/week (range, 2 – 16mg). The present mean DAS28ESR in MTX user and non-user was 2.81 +/- 0.95 and 2.84 +/- 1.88, respectively, and no differences were found between them. When 13 factors were selected and applied in a discrimination analysis, age, class, ILD grade, doses of PSL and SASP, use of other oral DMARDS, and eGFR were significant. Factors with small p value were ILD grade and eGFR. Correct discrimination rates for use and non-use of MTX were 79 % and 70 %, respectively. When multiple regression formula for the dose of MTX was calculated, significant coefficients were almost the same as those listed above. In conclusions, because we have not encountered big troubles in the use of MTX, it would be reasonable to decide the use of MTX taking these factors into considerations.

## W71-1

### Patient-based outcome assessment for the surgical reconstruction of the upper extremity in the patients with rheumatoid arthritis

Hajime Ishikawa, Asami Abe, Hiroshi Otani, Tomo Oyakawa, Kengo Harigane, Satoshi Ito, Daisuke Kobayashi, Satoru Kodama, Kiyoshi Nakazono, Akira Murasawa

Department of Rheumatology, Niigata Rheumatic Center, Shibata, Niigata, Japan

Conflict of interest: None

[Objectives] To clarify the effect of upper extremity surgeries for the patients with rheumatoid arthritis (RA), patient-based outcome assessment was performed prospectively. [Methods] Surgical reconstruction was performed in 40 patients with RA. The average age was 63 years old and the average duration of RA was 17 years. The site of operation was shoulder in one patient, elbow in 9, wrist in 22, and fingers in 8. The procedure was finger MP joint replacement (Swanson) in 19 joints, wrist synovectomy with Darrach procedure in 15, total elbow arthroplasty in 7, and others. Clinical assessment was performed using 6 methods before the surgery (baseline) and one year after the surgery. [Results] DAS28-ESR (4) and SDAI decreased from 3.9, 14.7 to 3.0, 7.7, respectively ( $p < 0.01$ ,  $p < 0.01$ ). DASH decreased from 50.4 to 39.7 ( $p = 3.9E-05$ ), HAQ-DI decreased from 1.3 to 1.13 ( $p < 0.01$ ), EQ-5D improved from 0.67 to 0.73 ( $p < 0.01$ ). However, BDI-II did not change (15.1 and 14.1,  $p = 0.16$ ). In the subgroup with unchanged or decreased medication (22 patients, 55%), the outcome was similar. [Conclusion] Upper extremity surgery for the patients with RA improved disease activity, disability in the upper extremity, physical function, and quality of life, despite unchanged mildly depressive condition.

## W71-2

### Correlation between patient-rated elbow evaluation (PREE) and other clinical parameters in patients with rheumatoid arthritis

Kenzo Hashizume<sup>1</sup>, Keiichiro Nishida<sup>1,2</sup>, Ryuichi Nakahara<sup>1</sup>, Ryozo Harada<sup>1</sup>, Takahiro Machida<sup>1</sup>, Masahiro Horita<sup>1</sup>, Toshifumi Ozaki<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Okayama University Hospital, <sup>2</sup>Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences

Conflict of interest: None

[Objectives] We aimed to investigate the correlation between patient-rated elbow evaluation (PREE) and other clinical parameters in rheumatoid patients treated by total elbow arthroplasty. [Methods] 26 elbows of 24 rheumatoid patients who underwent total elbow arthroplasty were included in this study. Average age (years old) was 63.6 and mean follow-up period (month) was 19.8, respectively. All patients were assessed by PREE, both elbow and forearm range of motion (ROM), DAS28-CRP, the scoring system of Japanese Orthopaedic Association elbow scoring system (JOA score), Disability of Arm, Shoulder, and Hand (DASH), Hand20, patients' satisfaction (mm), and HAQ-DI pre-and post-operatively. Spearman's correlation coefficients were examined between PREE and other clinical parameters. [Results] PREE significantly correlated with DAS28-CRP, DASH, Hand20, and HAQ pre-and post-operatively. Correlation between PREE and JOA score was significant preoperatively ( $p < 0.01$ ), but not significant postoperatively. [Conclusion] PREE did not significantly correlate with JOA score. PREE may not only reflect the elbow joint simply but also the whole function of upper extremity, because complex motions of upper extremity is required to satisfy most of the PREE questions for daily function.

## W71-3

### Effect of orthopaedic surgery on disease activity and physical function in patients with rheumatoid arthritis

Takahiro Iwata<sup>1</sup>, Hiromu Ito<sup>1,2</sup>, Moritoshi Furu<sup>1,2</sup>, Motomu Hashimoto<sup>2</sup>, Takao Fujii<sup>2,3</sup>, Noriyuki Yamakawa<sup>3</sup>, Chikashi Terao<sup>4</sup>, Wataru Yamamoto<sup>5</sup>, Masahiro Ishikawa<sup>1,2</sup>, Masayuki Azukizawa<sup>1</sup>, Yosuke Hamamoto<sup>1</sup>, Tsuneyo Mimori<sup>2,3</sup>, Shuichi Matsuda<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan, <sup>2</sup>Department of the Control for Rheumatic Diseases, Graduate School of Medicine, Kyoto University, <sup>3</sup>Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, <sup>4</sup>Center for Genomic Medicine, Graduate School of Medicine, Kyoto University, <sup>5</sup>Department of Health Information Management, Kurashiki Sweet Hospital

Conflict of interest: None

[Objectives] To examine the effectiveness of orthopaedic surgery in patients with rheumatoid arthritis (RA), we evaluated changes in disease activity and physical function after surgery. We explored the differences in effectiveness between replacement versus non-replacement, surgery in upper versus the lower limb. [Methods] Two hundredth and fourteen orthopaedic surgeries were performed in 168 patients. Disease activity score 28-ESR (DAS28-ESR) and modified Health Assessment Questionnaire (mHAQ) were examined just before surgery, at 6 months, and at 12 months after surgery. [Results] Significant improvement was seen for DAS28-ESR and mHAQ in upper and lower replacement, and upper non-replacement at 12 months follow-up. However, these in lower non-replacement did not change significantly. [Conclusion] Upper and lower replacement, and upper non-replacement surgery enhances the effects of improving not only systemic disease activity but also functional impairment.

## W71-4

### Analysis of parameters of the disease activity and functional measures of patients with rheumatoid arthritis undergoing surgery by using NinJa (National Database of Rheumatic Diseases by iR-net in Japan)

Kimio Masuda<sup>1</sup>, Toshihito Mori<sup>1</sup>, Mitsuyasu Iwasawa<sup>1</sup>, Satoru Ohashi<sup>1</sup>, Hiroshi Takamura<sup>1</sup>, Ryushi Marutani<sup>2</sup>, Toshihiro Matsui<sup>3</sup>, Jinju Nishino<sup>5</sup>, Shigeto Tohma<sup>4</sup>

<sup>1</sup>Department of Orthopaedic Surgery, National Hospital Organization Sagami Hospital, <sup>2</sup>Department of Rehabilitation, National Hospital Organization Sagami Hospital, <sup>3</sup>Department of Rheumatology, National Hospital Organization Sagami Hospital, <sup>4</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Na-

tional Hospital Organization Sagamihara Hospital, <sup>5</sup>Nishino Clinic, Orthopaedics and Rheumatology

Conflict of interest: None

[Objectives and Methods] We investigated the clinical data of patients undergoing surgery except joint arthroplasty from April 2012 through March 2013 by using NinJa (National Database of Rheumatic Diseases by iR-net in Japan) to examine the background of these patients and explore the effectiveness of these surgical procedures on the disease activity (DAS28) and functional measures (mHAQ). [Results] For this period, 234 patients underwent surgery, including upper extremities (group U, 74 cases), lower extremities (group L, 77 cases), spines (group S, 39 cases) and osteoporotic fractures (group O, 44 cases). The age at surgery was significantly higher in group O than other groups ( $p < 0.01$ ), and mHAQ was significantly higher in group O than group U and L, as well as in group S than group U, respectively. Although mHAQ improved in group U and L after surgery, it declined in group S and O. [Conclusion] These findings suggested that the timing to apply surgical treatment to RA patients could be important and critical for their better outcome and better QOL.

### W71-5

#### Effect of orthopaedic surgery on drug therapy in patients with rheumatoid arthritis

Takahiro Iwata<sup>1</sup>, Hiromu Ito<sup>1,2</sup>, Moritoshi Furu<sup>1,2</sup>, Motomu Hashimoto<sup>2</sup>, Takao Fujii<sup>2,3</sup>, Noriyuki Yamakawa<sup>3</sup>, Chikashi Terao<sup>4</sup>, Wataru Yamamoto<sup>5</sup>, Masahiro Ishikawa<sup>1,2</sup>, Masayuki Azukizawa<sup>1</sup>, Yosuke Hamamoto<sup>1</sup>, Tsuneyo Mimori<sup>2,3</sup>, Shuichi Matsuda<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Graduate School of Medicine, Kyoto University, <sup>2</sup>Department of the Control for Rheumatic Diseases, Graduate School of Medicine, Kyoto University, <sup>3</sup>Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, <sup>4</sup>Center for Genomic Medicine, Graduate School of Medicine, Kyoto University, <sup>5</sup>Department of Health Information Management, Kurashiki Sweet Hospital

Conflict of interest: None

[Objectives] To examine the effectiveness of orthopaedic surgery in patients with rheumatoid arthritis (RA), we examined changes in drug therapy after orthopaedic surgery. A kind of suitable medication and its dose were investigated. [Methods] Two hundredth and fourteen orthopaedic surgeries were performed in 168 patients at Kyoto University Hospital from January 2011 to May 2014. We explored the number of patients who used disease-modifying antirheumatic drugs (DMARDs), methotrexate (MTX), prednisolone (PSL), and biologics before and after surgery. The dose of MTX and PSL also investigated and differences between drug's does before versus after surgery was evaluated. [Results] The number of patients who used DMARDs, MTX, and PSL were decreased from preoperative to postoperative at 12 months respectively. However, the number of patients who used biologics was increased from preoperative to postoperative at 12 months. The mean dose of oral MTX increased from  $6.64 \pm 3.13$  mg/week to  $6.83 \pm 3.37$  mg/week at 12 months postoperatively. On the other hand, the mean dose of oral PSL significantly decreased from  $5.21 \pm 3.37$  mg/day to  $4.58 \pm 3.62$  mg/day at 12 months postoperatively ( $p = 0.0288$ ). [Conclusion] Orthopaedic surgery has possibility of reducing dose of PSL postoperatively.

### W71-6

#### Recent changes of rheumatoid knees in cases of total knee arthroplasty

Yuichi Mochida<sup>1</sup>, Katsushi Ishii<sup>1</sup>, Risa Matsumoto<sup>1</sup>, Yuki Ozawa<sup>1</sup>, Naoya Taki<sup>2</sup>, Naoto Mitsugi<sup>2</sup>, Tomoyuki Saito<sup>3</sup>

<sup>1</sup>Center for Rheumatic Diseases, Yokohama City University Medical Center, Yokohama, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Yokohama City University Medical Center, <sup>3</sup>Department of Orthopedic Surgery, Yokohama City University School of Medicine

Conflict of interest: Yes

[Objectives] The aim of this study was to investigate recent changes

of rheumatoid knee. [Methods] We analyzed the changes of radiological finding and clinical data with the information of medication in 203 TKA between 2000 and 2013 in our hospital. The Larsen grade, preoperative standing femoral-tibial angle (st-FTA), and the appearance of spur formation were observed. The dosages of methotrexate and prednisolone were also observed. [Results] In cases of TKA, the averaged Larsen grade did not show a yearly change. The averaged FTA showed no changes in each year. The increase of the case of RA knee with the spur formation was observed. The significantly increased dosage of methotrexate and the significantly downward medication of prednisolone dose by year were observed. [Conclusion] In our registry, the increased number of the cases with spur formation may reflect relative increase of RA knee which indicate the osteoarthritis-like change.

### W72-1

#### Early midterm follow-up results of K-NOW total elbow prosthesis in the patients of rheumatoid arthritis

Yu Sakuma, Mina Ishibashi, Tetsuji Hosozawa, Shinji Yoshida, Koichiro Yano, Katsunori Ikari, Shigeki Momohara

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Objectives] We use K-NOW prosthesis for total elbow arthroplasty (TEA) in RA patients, and we report the early midterm results of the prosthesis. [Methods] The 20 elbows of 20 RA patients who underwent TEA in our institution with a minimum 36 months follow-up period were reviewed (19 female and 1 male, 9 right side). Range of motion (ROM), JOA score, and DASH score were measured and calculated. Patient's satisfaction was assessed by using Visual Analogue Scale (VAS). X-ray films were examined to evaluate peri-implant radiolucent line (RLL), which was analyzed according to the type 0-IV classification of Morray et al. [Results] Mean follow up period was 54.8 (36.9–85.6) months, and the mean age at the operation was 61.2 (29.1–75.5) years old. Mean ROM of the operated elbow was 124.3 (100–138) degrees in flexion and -22.3 (-42–20) degrees in extension. JOA score, DASH score, and satisfaction was 75.9 (57–95), 36.0 (3.7–86) and 86.6 (17.5–100) % on average respectively, which were favorable on the whole. RLL was detected in 8 cases, and RLL of type III and IV was observed in 3 cases of cemented fixation humerus stem, causing little symptom. [Conclusion] K-NOW total elbow prosthesis brings favorable early midterm results in RA patients. Longer follow-up is needed to confirm these results.

### W72-2

#### Clinical results of revision and re-revision TEA for rheumatoid elbow

Yusuke Iwahori, Makoto Kurisuno, Yusuke Asano

Department of Orthopaedic Surgery, Aichi Medical University School of Medicine

Conflict of interest: None

[Objectives] We retrospectively evaluated the clinical results of revision and re-revision TEA for RA elbows. [Methods] We investigated 7 elbows of 6 RA patients (4 females and 2 males) underwent revision and re-revision TEA and followed up for average 34 months. There were 5 revision and 2 re-revision cases. All of initial TEA were Kudo elbows. The average age at the time of surgery was 61.6 years old at initial TEA, 70.2 at revision, 69.5 at re-revision. The reasons for revision were ulnar component loosening and olecranon fracture in 4 elbows, ulnar component loosening in 1 elbow, humeral component loosening in 1 elbow, and humeral component breakage in 1 elbow. There were revisions from Kudo to Kudo in 3 elbows, from Kudo to Morrey in 3 elbows, and from Morrey to Morrey in 1 elbow. Iliac bone graft in all elbows and internal fixation of the olecranon in 4 elbows were performed simultaneously. [Results] There were skin troubles around olecranon in 2 elbows. No component loosening was observed at the final visit. The average range at the final visit were 132 degrees in flexion, -35 in extension, 71 in pronation, and 73 in supination. The averaged JOA score at the final visit was 81.4. [Conclusion] We could achieve good elbow function by revision or re-revision TEA in the all cases.

### W72-3

#### The assessment of change in Range Of Motion (ROM) with time after Linked Total Elbow Arthroplasty

Hiroko Ogino<sup>1</sup>, Hiromu Ito<sup>1</sup>, Moritoshi Furu<sup>2</sup>, Masahiro Ishikawa<sup>2</sup>, Masayuki Azukizawa<sup>1</sup>, Yosuke Hamamoto<sup>1</sup>, Hiroyuki Yoshitomi<sup>3</sup>, Shuichi Matsuda<sup>1</sup>

<sup>1</sup>The Department of Orthopaedic Surgery, Kyoto University Graduate School of Medicine, <sup>2</sup>The Department of the Control for Rheumatic Diseases, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>3</sup>The Center for Innovation in Immunoregulative Technology and Therapeutics, Kyoto University Graduate School of Medicine, Kyoto, Japan

Conflict of interest: None

[Objectives] We did a retrospective study, to assess change in ROM with time, especially for extension and flexion, in patients with Rheumatoid arthritis (RA) and Osteoarthritis (OA) after linked TEA. RA patients were further divided into subgroups according to Larsen grade to evaluate and compare ROM between each grade. [Methods] We included a consecutive series of patients who underwent linked TEAs performed at our institution from 2008 to 2013. There were five male and 23 female patients. We assessed postoperative extension and flexion after six months, and every other year thereafter. Subgroup analysis was performed after RA patients were divided into subgroups according to Larsen grade to see whether there is any significant difference in the ROM between each grade. [Results] We compared the ROM in two groups. Extension were less favorable in patients with RA than in OA patients after 3 years of follow-up. On the other hand, flexion and extension were maintained for a few years after surgery in two groups. There were not significant differences between each grade in change in ROM with time. [Conclusion] These results shows that ROM in patients with the worst-grade RA were improved and maintained after TEA, We believe that TEA is an effective treatment in progressive RA patients.

### W72-4

#### Postoperative stability of the rheumatoid wrist after the Sauvé-Kapandji procedure

Ryo Oda, Daigo Taniguchi, Shogo Toyama, Daisaku Tokunaga, Tetsuro Yamasaki, Maki Asada, Hiroyoshi Fujiwara, Toshikazu Kubo  
Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine

Conflict of interest: None

[Objectives] The Sauvé-Kapandji (S-K) procedure is commonly performed to treat wrist in patients with rheumatoid arthritis (RA). We conducted a retrospective study of postoperative wrist stability in patients treated with the S-K procedure alone. [Methods] We evaluated the clinical course of 55 hands (48 subjects) for 5 years after the S-K procedure. The mean age was 55.4 yo, with a mean duration of RA of 90.7 months. We evaluated the severity of carpal translocation and bony ankylosis of the radiocarpal and midcarpal joints at the preoperative and final assessment. [Results] There was a statistically significant progression of carpal collapse and ulnar translation. No significant progression of palmar carpal translation, and there were no cases of radiocarpal dislocation at the final assessment. No significant development of carpal translocation was seen in subjects with preoperative bony ankylosis. [Conclusion] In this study, we reviewed the long-term outcomes of the S-K procedure performed in isolation for wrists without radiocarpal dislocation. Our results demonstrated that the post-operative wrist by Sauvé-Kapandji procedure would have stability of carpal bones.

### W72-5

#### Clinical outcome of total shoulder arthroplasty in patients with rheumatoid arthritis treated by biologics

Katsuaki Kanbe, Junji Chiba, Yasuo Inoue, Masashi Taguchi, Akiko Yabuki  
Department of Orthopaedic Surgery, Tokyo Women's Medical University, Medical Center East

Conflict of interest: None

[Objectives] However biologics are effective to inhibit bone and joint damage in rheumatoid arthritis (RA), there is no evidence in clinical outcome of total shoulder arthroplasty (TSA) treated with biologics. Here we report the clinical outcome of modular typed TSA in short term. [Methods] 11 RA patients with mean age of 68.1 years, mean CRP of 1.39 mg/dl, mean MMP-3 of 127.9 ng/ml, mean serum TNF- $\alpha$  of 80.7 pg/ml, mean serum IL-6 of 21.7 pg/ml underwent the modular typed TSA by using Lima (SMR®). JOA scores were compared after TSA at mean follow-up period of 9.4 months. [Results] JOA score was improved from 39.3 to 77.7 points significantly. Glenoid component was stable if bone stock was sufficient, however we experienced a revision of loosening glenoid loosening component [Conclusion] Under biologics treatment, there is no case of infection after TSA. It was important to develop the sufficient glenoid view and stabilized repair of rotator cuff firmly.

### W72-6

#### Clinical result of lumbar spondylolisthesis for rheumatoid arthritis patients

Junya Mibe<sup>1</sup>, Kengo Yamamoto<sup>2</sup>

<sup>1</sup>Tokyo Metropolitan Ohtsuka Hospital, <sup>2</sup>Tokyo Medical University

Conflict of interest: None

[Objectives] We investigated operative result of lumbar spondylolisthesis for rheumatoid arthritis patients. [Methods] Fifteen patients had undergone surgical treatment at our hospital between 1999 to 2012, and who had been followed 18 months to 10 years (mean 6 years). All patients were women (mean age 66 years; range 47-85 years). Preoperative symptoms were cauda equina disorder 6 patients (L3/4:1, L3/4 + L4/5:1, L4/5:4) radiculopathy 9 patients (L3 root disorder cause of L3/4:1, L4 root disorder cause of L4/5:2, L5 root disorder cause of L4/5:4, L4 and L5 roots disorder cause of L3/4 and L4/5:1, L5 root disorder cause of L5/S:1. Operative methods were PLIF: 7 patients, pedicle screw (PS) + PLF: 4 patients, fenestration: 3 patients, PLF:1 patient. [Results] JOA score was 11 points preoperatively, and 16 points at the time of final follow up. In X-ray at the final follow up, we recognized clear zone of PS: 4 patients, pseudarthrosis of PLIF: 1 patient, spondylolisthesis of adjacent intervertebral joint: 6 patients, compression fracture: 7 patients. Two patients had pain because of adjacent intervertebral joint. [Conclusion] Use of instruments of lumbar spondylolisthesis for rheumatoid arthritis patients is useful, but we need care for clear zone of PS and adjacent intervertebral joint.

### W73-1

#### Prediction factors at early phase for clinical response with infliximab for rheumatoid arthritis

Satoko Hayashi, Katsuya Suzuki, Keiko Yoshimoto, Masaru Takeshita, Takahiko Kurasawa, Tsutomu Takeuchi  
Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] Serum trough level of infliximab (IFX) and plasma IL-6 levels at 1 year determined remission by IFX. Aim is to elucidate factors for predicting clinical response in daily practice. [Methods] We studied 35 RA treated with IFX (3-9 mg/kg, every 4-8 weeks) based on T2T. Serum IFX trough level and 9 cytokines were measured at baseline, 14 and 22 weeks. Associations between these parameters and clinical data were statistically analyzed. [Results] Patients were classified into 4 groups by values of IFX trough and IL-6. At early phase, remission rates were the highest and DAS28-ESR was the lowest in high IFX and low IL-6 group as with above report. Next, serum cytokines at baseline and DAS28-ESR at 1 year were analysed. Serum IL-6 and IL-10 correlated to DAS28-ESR. Low IL-6 and IL-10 were associated to low DAS28-ESR. Cut off values of IL-6 and IL-10 (5.45 and 1.68 pg/ml) discriminated at DAS28-ESR remission or non-remission with high sensitivity and moderate specificity. [Conclusions] Disease activity and remission at early phase after IFX induction were associated with serum trough IFX and IL-6. Serum IL-6 and IL-10 levels at baseline predict the effect of IFX at 1 year, and more intensive therapy may be needed in patients with high serum IL-6 and IL-10 at baseline.

### W73-2

#### Examination of the relevance of the golimumab administration efficacy and serum cytokine concentration for Juntendo University hospital rheumatoid arthritis patients

Nagachika Sugisaki<sup>1</sup>, Michihiro Ogasawara<sup>1</sup>, Naoto Tamura<sup>1</sup>, Tomoko Ito<sup>1</sup>, Ran Matsudaira<sup>1,2</sup>, Takashi Watanabe<sup>1</sup>, Fumio Sekiya<sup>1</sup>, Kurisu Tada<sup>1</sup>, Kentaro Minowa<sup>1</sup>, Ken Yamaji<sup>1</sup>, Yoshinari Takasaki<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology Juntendo University School of Medicine, Tokyo, Japan, <sup>2</sup>Department of Internal Medicine Kyoundo Hospital, Tokyo, Japan

Conflict of interest: None

**[Objective]** We examined the relationship of clinical effect and cytokine concentration Golimumab (GLM) effectiveness for administered rheumatoid arthritis (RA) patients, **[Methods and Patients]** All of 71 patients were started to receive subcutaneous injections every 4 weeks of GLM. And measured 10 patient serum cytokine concentration of using a Beads array system before start and after the 52 weeks. **[Results]** Among all patients, 90% were female, DAS28 remission patients (score<2.3) at week 52 was 56.1%. The mean score of DAS28 at baseline, 52 were 3.9±1.2, 2.1±0.8. In addition, serum IL-6 concentration showed an onset before 21.33pg/ml, 52 weeks after 8.55pg/ml and improvement (p<0.03). Also showed a significant reduction observed correlation between  $\Delta$ DAS and  $\Delta$ IL-6 (p = 0.03). Our result suggests that GLM was effective at the early weeks, and serum IL-6 concentration was reduced. **[Conclusion]** GLM administration is validity from the administration early, we showed also high continuation rate after 52 weeks, also high DAS28-CRP remission achievement rate, and correlate to the decrease IL-6 concentration and decreased disease activity. Future, serum cytokine and chemokine concentration measurement more number of cases, we plan to examine the correlation between the clinical effect.

### W73-3

#### Assessing Adalimumab trough level to reach remission/low disease activity in RA patients and biomarker to achieve the ADA trough level ~ multivariate analysis~

Masamitsu Natsumeda<sup>1</sup>, Koji Takasugi<sup>1</sup>, Misuzu Yamashita<sup>1</sup>, Kazuhiko Ezawa<sup>1</sup>, Yoshihisa Nasu<sup>2</sup>, Wataru Yamamoto<sup>3</sup>, Keiichiro Nishida<sup>4</sup>

<sup>1</sup>Department of Internal Medicine, Center of Rheumatology, Kurashiki Sweet Hospital, Kurashiki, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Center of Rheumatology, Kurashiki Sweet Hospital, Kurashiki, Japan, <sup>3</sup>Department of Clinical Information Management, Kurashiki Sweet Hospital, Kurashiki, Japan, <sup>4</sup>Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Conflict of interest: None

**[Objectives]** Although it is true for all bDMARDs, efficacy of Adalimumab (ADA) on RA patients is critically influenced by Anti-Adalimumab Antibody (AAA). The aim of our study is to investigate optimal ADA trough level to reach remission/LDA and search for biomarker to achieve the ADA trough level. **[Methods]** 56 RA patients treated with ADA through Sep 2008 to July 2010 at our center are subjects for analysis on DAS-ESR, CRP, MMP3, and the other serological markers prior and throughout treatment. After 4 weeks of first ADA administration, ADA trough level and AAA were measured at Sanquin Diagnostics Inc. Association of disease activity for 41 patients without AAA and ADA trough level was analyzed by multivariate analysis. **[Results]** ROC analysis showed that ADA trough level to achieve REM/LDA is 9 $\mu$ g/mL. An associated factor to reach the trough level is MMP-3, cut-off value of 148.6, when ADA is first administered. **[Conclusion]** Our analysis showed relatively higher ADA trough level than previously reported. This could explain that loss of efficacy in patients without AAA is attributed to lower ADA trough level and further investigation is necessary for the high trough level, 9 $\mu$ g/mL. MMP-3 may be a useful marker to predict good efficacy and to reach high ADA trough level.

### W73-4

#### Influence of premedication with corticosteroids on infliximab therapy in patients with rheumatoid arthritis

Yusuke Kashiwado<sup>1</sup>, Ayumi Uchino<sup>1</sup>, Kensuke Oryoji<sup>3</sup>, Kazuhiko Higashioka<sup>3</sup>, Kenji Yoshida<sup>3</sup>, Kazuo Kamada<sup>3</sup>, Shinichi Mizuki<sup>3</sup>, Eisuke Yokota<sup>3</sup>, Toshiyuki Ota<sup>2</sup>, Shuji Nagano<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Aso Iizuka Hospital, <sup>2</sup>Center for Rheumatic Disease, Aso Iizuka Hospital, <sup>3</sup>Division of Rheumatology, Matsuyama Red Cross Hospital

Conflict of interest: None

**[Objectives]** To evaluate the efficacy and safety of premedication with corticosteroids on infliximab therapy in patients with rheumatoid arthritis. **[Methods]** We analyzed the patients who were administered infliximab for rheumatoid arthritis in our two hospitals from January 2008 to November 2013, retrospectively. Patients were classified into two groups whether corticosteroids were given before infliximab injections or not. Drug survival, time to recurrence, the duration of continuous infliximab treatment after the first recurrence, the rate of infusion reactions and other side effects were evaluated. **[Results]** 63 patients were pretreated and 72 were not. Baseline characteristics, the rate of infusion reactions and other side effects, and time to recurrence were comparable in the two groups. Drug survival and the duration of continuous infliximab therapy after the first recurrence were longer in the pretreated group (log rank test, p<0.01). The patients pretreated with corticosteroids at the time of increasing infliximab dosage and shortening infusion intervals discontinued infliximab after remission more frequently, and after secondary failure less than the others. **[Conclusion]** Premedication with corticosteroids may improve the response when infliximab treatment is weakening.

### W73-5

#### Inhibitory effects of biologic agents on large joint-destruction in patients with rheumatoid arthritis and the risk factors of progression in joint-destruction

Arata Nakajima, Masato Sonobe, Shinji Taniguchi, Koichi Nakagawa  
Department of Orthopedics, Toho University School of Medicine, Sakura, Japan

Conflict of interest: None

**[Objectives]** Many clinical trials tell us that biologic agents inhibit small joint-destruction, however, there have been a few reports demonstrating inhibitory effects on large joint-destruction. **[Methods]** Seventy-seven patients receiving a biologic agent for a year or more are included in this study. The mean age at initiating the latest biologic agent was 61.5 year-old, and a total of 290 joints including shoulder, elbow, hip, knee, and ankle joints were evaluated whether there was progression in joint-destruction comparing the radiographs before and after treatment. **[Results]** DAS28/ESR was significantly improved from 4.60 to 2.52 after treatment (p<0.01). Progression in joint-destruction was found in 13 patients (17%) and 16 joints (5.5%), and joints on Larsen grade III/IV showed significantly higher progression rate than those on grade I/II (p<0.01). Multiple regression analyses showed that Larsen grading at initiating biologic agents was a risk factor for progression in joint-destruction (odds ratio = 2.935). **[Conclusion]** Because progression in large joint-destruction is affected by the extent of bone destruction of individual joint, X-ray examinations for large joints at initiation of biologics are required.

### W73-6

#### The prospective evaluation of structural damage of large joints in patients with rheumatoid arthritis medicated biological DMARDs for two years

Atsushi Kaneko, Hiroyasu Kanda, Yosuke Hattori, Daihei Kida  
Dept. of Orthop. Surg. And Rheumatology, Nagoya Medical Center, National Hospital Organization

Conflict of interest: None

**[Objectives]** The purpose of this study is to evaluate of structural damage of large joints in patients with rheumatoid arthritis medicated bi-

ological DMARDs for two years [Methods] The ARASHI scoring system devised new radiographic scoring systems (Status score; range 0-16 points, and Change score; range -11 to 12 points) for evaluation of large joints with RA. Radiographs showing anterior/posterior views of large joints (shoulder, elbow, hip, knee, and ankle joints) taken in two years were collected from 127 patients, 1217joints with established RA [Results]4joints were improved over 2 points, 32 were improved 1points, 1123 joints revealed no change, 42joints were getting worse 1points, and 7joints were getting worse over 2points. [Conclusion] The results suggest that the ARASHI scoring method might be useful for the assessment of status, as well as longitudinal monitoring of destruction and remodeling of large joints with RA.

#### W74-1

##### **Efficacy and safety of etanercept in rheumatoid arthritis patients over 75 years old**

Satoru Kodama<sup>1,2</sup>, Satoshi Ito<sup>1</sup>, Daisuke Kobayashi<sup>1</sup>, Tomo Oyakawa<sup>3</sup>, Kengo Harigane<sup>4</sup>, Asami Abe<sup>1</sup>, Hiroshi Otani<sup>1</sup>, Hajime Ishikawa<sup>1</sup>, Akira Murasawa<sup>1</sup>, Yuichi Makino<sup>2</sup>, Masakazu Haneda<sup>2</sup>, Kiyoshi Nakazono<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Niigata Rheumatic Center, Niigata, Japan, <sup>2</sup>Division of Metabolism and Biosystemic Science, Department of Medicine, Asahikawa Medical University, <sup>3</sup>Department of Orthopedic Surgery, University of the Ryukyus, <sup>4</sup>Department of Orthopedic Surgery, Yokohama City University

Conflict of interest: None

[Objectives] Early introductions of biologics in early RA patients are well documented, but there are few reports of biologics use in established elderly RA patients. We used ETN, which has a short half-life and was considered safe, for elderly RA patients. [Methods] Out of 336 patients treated with ETN at Niigata Rheumatic Center from May 2008 to March 2014, clinical course and data of the patients who started ETN at 75 years old (YO) or older were analyzed. The efficacy and safety of ETN was evaluated at 24 months. [Results] Forty eight patients (18 males, 30 females), a mean age of 79.0 ±2.9 YO were analyzed. Fifty percent of the patients did not inject by themselves and were injected by family or by general practitioners. Clinical parameters such as articular findings, serum marker, disease activity score and so on, improved significantly. Adverse events occurred in 11 patients. Seven patients stopped ETN and 4 out of them had infection. One patient (85YO) died due to tuberculosis (TB) and another (80YO) died due to pneumocystis pneumonia (PCP) and another (82YO) died due to lung cancer. [Conclusion] We consider that ETN is an effective and relatively safe treatment for elderly RA patients. Prevention of TB, PCP and pneumococcal pneumonia should be considered.

#### W74-2

##### **Infections during the treatment by biologic DMARDs and their continuation or discontinuation**

Tamao Nakashita<sup>1</sup>, Akira Jibatake<sup>1</sup>, Kotaro Matsumoto<sup>1</sup>, Akira Yoshida<sup>1</sup>, Yuto Hamada<sup>1</sup>, Daisuke Kato<sup>2</sup>, Yoshiaki Kuga<sup>3</sup>, Tamio Takahei<sup>3</sup>, Shinji Motojima<sup>1</sup>

<sup>1</sup>Kameda Medical Center, Rheumatology and Allergy, Kamogawa, Japan, <sup>2</sup>Kato Daisuke Clinic, <sup>3</sup>Tateyama Orthopedic Clinic

Conflict of interest: None

Patients who had infectious disease events (IDEs) during the treatment with biologic DMARDs (bDMARDs) were picked up from the clinical charts and analyzed. IDEs were defined as events which needed specific antimicrobial treatments and severe IDEs (SIDEs) were defined as those which needed hospitalizations. The number of patients who were treated with bDMARDs were 252, however because some patients changed bDMARDs, total 431 bDMARDs were used. Total durations of bDMARDs use were 7448 months, and the numbers IDEs (including SIDEs) and SIDEs were 283 and 41, respectively during the period. The incidences of IDEs and SIDEs were 44.6/100 patients year and 6.6/100 patients year, respectively. The most prevalent site of infection was respiratory system accounting more than 50%. There were no differences in the incidence of IDEs and SIDEs among 7 bDMARDs, however, the incidence of bacterial cutaneous and subcutaneous infection was signifi-

cantly higher in tocilizumab. PCP and pulmonary cryptococcosis were found only in TNF-inhibitor users. Three patients died of SIDEs. The managements of bDMARDs after SIDEs were as follows; continuation 18, discontinuation including patients' death 16, reintroduction after short term discontinuation 7.

#### W74-3

##### **QuantiFERON assay results and tuberculosis outbreaks in RA patients during biologics therapy**

Toshiaki Shimizu, Yuko Takahashi, Hiroyuki Yamashita, Hiroshi Kaneko, Akio Mimori

Division of Rheumatic Diseases, National Center for Global Health and Medicine

Conflict of interest: None

**Objectives:** To estimate QuantiFERON (QFT) assay results and tuberculosis/Tb outbreaks in RA patients during biologics therapy. **Methods:** Retrospective study using our 978 RA database including 211 follow-up patients on biologics therapy. **Results:** 185 patients were examined for QFT-TB gold assay during or before starting biologics therapy, and the results were positive in 12, boundary in 10, or indeterminate in 4, which were further monitored for QFT. Of the 12 positive patients, the QFT before biologics treatment were positive (2), a history of Tb (1), unknown (5), boundary (1), or negative (3). Of these, 4 patients that showed positive conversion had been treated by infliximab or abatacept, and adjunctive MTX (4) and prednisolone (3). Nine of 14 patients having initially boundary QFT results showed conversion to positive (1) or negative (8). Seven of the 8 indeterminate results showed negative conversion. Tb-outbreaks were found in none of the above patients but in 4 patients outside GFT estimation. Two of the 4 Tb developed 3 or 5 years after INH prophylaxis, and other one patient showed negative tuberculin test and no radiological abnormality before biologics therapy. **Conclusion:** QFT results may change during biologics therapy and should be monitored carefully.

#### W74-4

##### **Clinical manifestation and DMARDs therapy after malignant lymphoma involving MTX-LPD in patients with rheumatoid arthritis**

Atsushi Kaneko<sup>1</sup>, Hiroyasu Kanda<sup>1</sup>, Yosuke Hattori<sup>1</sup>, Daihei Kida<sup>1</sup>, Masao Katayama<sup>2</sup>

<sup>1</sup>Dept. of Orthop. Surg. And Rheumatology, Nagoya Medical Center, National Hospital Organization, <sup>2</sup>Dept. of Rheumatology and Collagen Disease, Nagoya Medical Center, National Hospital Organization

Conflict of interest: None

[Objectives] The purpose of this study is to evaluate the clinical manifestation and DMARDs therapy after malignant lymphoma involving MTX-LPD in patients with rheumatoid arthritis [Methods] We investigated 28RA patients complicated malignant lymphoma involving MTX-LPD and investigated items were pre-medicated DMARDs before diagnosis of ML, cellular type of ML, chemotherapy for ML, prognosis of these patients and post-medicated DMARDs after ML therapy. [Results] Pre-medicated DMARDs of 28 patients were 23 MTX, 5 other cs-DMARD (BUC2, TAC2, SSS1). 13 Biologics user were IFX5, GLM3, ADA2, ETN1, ABT2 with MTX. Cellular type of 21patients were DLB-CL. 15 patients were underwent R-CHOP chemotherapy and 13 patients is not underwent. 1 patient was deceased, and the others is alive. Post-medicated DMARDs after ML therapy were 6 tocilizumab, 8 iguratimod, 3 Tacrolimus and 7 no DMARDs. [Conclusion] The prognosis of ML and MTX-LPD is getting better, but the selection of post-medicated DMARDs after ML is difficult and no evidence.

#### W74-5

##### **Evaluation of past hepatitis B virus (HBV) infection in rheumatoid arthritis patients treated with immunosuppressant and biologics DMARDs**

Masaomi Yamasaki

Division of Rheumatology, Shin-Yokohama Yamasaki Clinic

Conflict of interest: None

[Objectives] The aim of this study was to examine the safety of immunosuppressant and biologics DMARDs therapy in patients with rheumatic disease and past hepatitis B virus (HBV) infection. [Methods] Patients with past HBV infection were included in the study. All patients showed hepatitis B surface antibodies (anti-HBs) and of negative serum HBV DNA. Using immunosuppressive DMARDs were 1219 MTX, 82 TAC and biologic DMARDs were 55 infliximab, 213 etanercept, 53 adalimumab, 48 tocilizumab and 20 abatacept. [Results] 217 out of 1594 cases showed HBsAg-negative and anti-HBc-positive serology indicative of past HBV infection. There were no reactivation of HBV in MTX or TAC treated RA. In 14 RA treated with biologics DMARDs, two viral reactivation was observed in patients while using MTX with infliximab. However all of them showed elevation of HBV-DNA, only one showed elevation of aminotransferase. Withdrawal of biologics and treated with entecavir in these two patient, it showed negative HBV-DNA again and no development of acute hepatitis nor fulminant hepatitis. [Conclusion] Regular monitoring of both serum aminotransferase levels and HBV-DNA were useful to detect reactivation of HBV.

#### W74-6

##### A questionnaire survey for the patients with home injection of biologics, The first report

Natsuko Inoue<sup>1</sup>, Michiyo Moriyama<sup>1</sup>, Takefumi Furuya<sup>2</sup>, Hisashi Yamanaka<sup>2</sup>

<sup>1</sup>Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, <sup>2</sup>Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Purpose] Role of nurses has become important in the patient education program along with the increasing number of patients with home injection of biologics. To elucidate the issues of home biologics injection program, we conducted a questionnaire survey. [Method] All patients with home injection and visited our institute from August to October 2014 were asked to participate in this survey, and after the informed consent, twenty-six questions were asked. [Results] Four hundreds thirty RA patients participated in this survey. All patients satisfied with the current management, could understand the introduction of home injection, and satisfied with training hours. 65% had any anxiety for home injection, but all felt reasonable after starting home injection. Home injection decreased the hospital visit, increased the flexibility of injection. They also felt that home injection is easier than expected. 34% have anxiety for the use of biologics, including continuance, side effects, and economic issues. 35% recognized social support system, but only 16% recognized those of our hospital. [Conclusion] Patient education program of home injection has been going well so far. However, from the prospect of home health care, consults of daily living by medical team would be necessary.

#### W75-1

##### Osteoporosis in Rheumatoid arthritis patients

Yoichi Toyoshima, Takashi Nagai, Osamu Namiki, Koei Oh, Katsunori Inagaki

Department of Orthopaedic Surgery, Showa University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] Postmenopausal rheumatic arthritis patients who matched age and medication in osteoporosis were compared with postmenopausal healthy women. [Methods] The mean age was 73.3 y.o. We measured with bone density of the lumbar vertebrae A-P, femoral neck and forearm. Rheumatic disease activity was evaluated with SDAI. About blood test, CRP, MMP-3, TRACP-5b, P1NP, ucOC and Pentosidine were measured. Morphometric vertebral fractures were evaluated in X-ray. [Results] With Bone density, conspicuous distinction was not found with healthy woman with RA patient. Significant difference was not found between two groups in bone-related marker either. Pentosidine value was significantly high in healthy woman group in comparison with RA group ( $P < 0.05$ ). Significantly much morphometric vertebral fracture was found

about RA group. In RA group, difference was not recognized to bone density and bone-related marker in comparison with postmenopausal woman of same generation either. However, morphometric vertebral fracture was found a lot in RA group. [Conclusion] In osteoporosis with RA, there is case which bone fracture risk that cannot be evaluated cannot be detected only with bone density and existing bone-related marker, or cannot be evaluated.

#### W75-2

##### The prevalence and the analysis of the clinical characteristics of the vertebral fracture in patients with rheumatoid arthritis

Yusuke Sugimura<sup>1</sup>, Naohisa Miyakoshi<sup>2</sup>, Seiya Miyamoto<sup>3</sup>, Michio Hongo<sup>2</sup>, Yuji Kasukawa<sup>2</sup>, Natsuo Konishi<sup>4</sup>, Takeshi Kashiwagura<sup>5</sup>, Masakazu Urayama<sup>6</sup>, Moto Kobayashi<sup>7</sup>, Tsutomu Sakuraba<sup>7</sup>, Hiroki Ito<sup>8</sup>, Toshiaki Aizawa<sup>9</sup>, Hiroshi Aonuma<sup>10</sup>, Yoichi Shimada<sup>2</sup>

<sup>1</sup>South Akita Orthopedic Clinic, Akita, Japan, <sup>2</sup>Department of Orthopedic Surgery, Akita University Graduate School of Medicine, Akita, Japan, <sup>3</sup>Department of Orthopedic Surgery, Nakadori General Hospital, Akita, Japan, <sup>4</sup>Department of Orthopedic Surgery, Akita Kousei Medical Center, Akita, Japan, <sup>5</sup>Department of Rehabilitation Medicine, Akita City Hospital, Akita, Japan, <sup>6</sup>Department of Orthopedic Surgery, Ogachi Central Hospital, Akita, Japan, <sup>7</sup>Department of Orthopedic Surgery, Hiraka General Hospital, Akita, Japan, <sup>8</sup>Department of Orthopedic Surgery, Yamamoto Kumiai General Hospital, Akita, Japan, <sup>9</sup>Department of Orthopedic Surgery, Kita Akita Municipal Hospital, Akita, Japan, <sup>10</sup>Department of Orthopedic Surgery, Kakunodate Municipal Hospital, Akita, Japan

Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) is one of the causes of secondary osteoporosis. We investigated the prevalence and the clinical characteristics of vertebral fractures in RA patients. [Patients and Methods] In Akita orthopedic group on rheumatoid arthritis (AORA registry), 85 patients (all women, Mean age 67.6 (41-84) years, mean duration of illness 10.6 (2-63) years), who were examined with radiograph, were included in this study. We evaluated the prevalence of vertebral fracture and analyzed the clinical characteristics. [Results] Prevalence of vertebral fractures was 28.2%. The patients with vertebral fractures had the age of 72.3±8.3 years (without vertebral fractures, 65.7±10.0 years), the dose of PSL of 3.1±2.6mg/day (without vertebral fractures, 1.6±2.1mg/day). Age and dose of PSL were higher in patients with vertebral fractures than patients without vertebral fractures ( $p < 0.01$ ). There was no significant difference about duration of illness, disease activity or bone mineral density between patients with vertebral fractures and without. [Conclusion] Prevalence of vertebral fractures in patients with rheumatoid arthritis was 28.2%. Patients with vertebral fractures had high age and high dose of PSL.

#### W75-3

##### Outcomes of applying the new guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research in Japanese patients with rheumatoid arthritis

Takefumi Furuya, Atsuo Taniguchi, Shigeki Momohara, Hisashi Yamanaka  
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Objectives] We applied the new guidelines on the management and treatment of glucocorticoid-induced osteoporosis (GIO) of the Japanese Society for Bone and Mineral Research (JSBMR) and evaluated the clinical utility in Japanese patients with rheumatoid arthritis (RA). [Methods] We studied 5,852 Japanese patients with RA who participated the 27th IORRA cohort study in October and November 2013 with the guideline without the information of lumbar bone mineral density. [Results] Among the patients with RA, 1,944 patients (35%) were treated with glucocorticoids. Among the patients treated with glucocorticoids, 1,203 patients (62%) would be offered osteoporosis treatments according to the guideline. Among the 1,203 patients, only 395 patients (33%) were treated with the first-line treatment (alendronate and risedronate) and only 517 patients (43%) were treated with the first-line and the alternative

(teriparatide, ibandronate, alfacalcidol, and calcitriol) treatments. [Conclusion] The clinical utility for the new guidelines on the management and treatment of GIO of the JSBMR appears to be high in Japanese patients with RA. A substantial gap exists between fracture risk and osteoporosis treatment in Japanese patients with RA as reported previously.

#### W75-4

##### Evaluation of guidelines on the management and treatment of glucocorticoid-induced osteoporosis (2014 update) and prior fragility fracture

Taketoshi Kushida<sup>1,2</sup>, Yusuke Ueda<sup>1,2</sup>, Yoshio Ozaki<sup>2</sup>, Yonsu Son<sup>2</sup>, Takahiko Wada<sup>1,2</sup>, Hirokazu Iida<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Kansai Medical University Hirakata Hospital, Osaka, Japan, <sup>2</sup>Department of Rheumatology and Clinical Immunology, Kansai Medical University Hirakata Hospital, Osaka, Japan

Conflict of interest: None

[Objectives] The aim of this study was to evaluate between guidelines on the management and treatment of glucocorticoid-induced osteoporosis (2014 update) and prior fragility fractures. [Methods] We analyzed the scores consisted of prior fragility fractures, age, glucocorticoid (GC) dose, lumbar bone mineral density (BMD) in 241 patients who were treated with GC from January 2014 through March 2014 at our hospital. The major underlying diseases were rheumatoid arthritis and rheumatoid arthritis (57.7%) and systemic lupus erythematosus (33.6%). [Results] In the low risk group ( $0 \leq \text{score} \leq 2$ ), the averages were score: 1.0 points, age: 40.5 years, GC: 4.9mg/day, %YAM: 104%, fragility fractures rates: 0%. On the other hand, in the high risk group ( $3 \leq \text{score} \leq 19$ ), the averages were score: 9.1 points, age: 62.1 years, GC: 6.4 mg/day, %YAM: 85.7 %, fragility fractures rates: 50%. The rate of the prior fragility fracture was 50% in the group of eight points and furthermore, it was increasing to 100% in the group of ten points. [Conclusion] The updated guideline was thought as a useful tool for the management of glucocorticoid-induced osteoporosis.

#### W75-5

##### Utility of QCT/FEM in Glucocorticoid-Induced Osteoporosis

Miho Oshima<sup>1</sup>, Hiroko Kanda<sup>2</sup>, Masahiko Bessho<sup>3</sup>, Shoko Tateishi<sup>2</sup>, Kanae Kubo<sup>1</sup>, Isao Ohnishi<sup>3</sup>, Kazuhiko Yamamoto<sup>1</sup>

<sup>1</sup>Department of Allegology and Rheumatology, Hospital of Tokyo University, Tokyo, Japan, <sup>2</sup>Department of Immunotherapy Management, Graduate School of Medicine, Tokyo, Japan, <sup>3</sup>Department of Orthopaedic Surgery, Kaken Hospital, Clinical Medical Research Center, International University of Health and Welfare, Tiba, Japan

Conflict of interest: None

[Objectives] The utility of BMD by DXA is limited, and bone strength is being focused in glucocorticoid-induced osteoporosis (GIO). QCT-based finite element method (QCT/FEM) and hip structural analysis (HSA) by DXA are known to measure the bone strength. We examined the utility of bone strength prospectively. [Methods] 28 patients with autoimmune disease who had received no treatment of osteoporosis, and would start glucocorticoid (GC) therapy were enrolled. Treatments of osteoporosis were decided by physicians in charge. BMD, QCT, HSA and bone metabolic and strength markers were examined at the start of steroid, after 4 and 12 months. [Results] Vertebral strength index (VSI) in QCT significantly decreased after starting GC ( $p=0.004$ ). On the other hand, there were no significant difference in HSA and BMD. 3 patients developed vertebral compression fractures (Fx). Bone markers had no significant difference between receiving bisphosphonate therapy or not, or decreasing of VSI. [Conclusion] VSI by QCT has a possibility to be a predictive factor of vertebral Fx. This study included a small number of patients, so larger prospective trial is warranted to confirm the utility of QCT/FEM.

#### W75-6

##### A retrospective analysis of bone mineral density in patients with juvenile-onset autoimmune diseases using steroids

Yuzaburo Inoue<sup>1</sup>, Kanako Kudo<sup>1</sup>, Takeshi Yamamoto<sup>1</sup>, Koki Chiba<sup>2</sup>,

Yoshinori Morita<sup>3</sup>, Taiji Nakano<sup>4</sup>, Fumiya Yamaide<sup>1</sup>, Takayasu Arima<sup>2</sup>, Minako Tomiita<sup>5</sup>, Naoki Shimojo<sup>1</sup>

<sup>1</sup>Department of Pediatrics, Graduate School of Medicine, Chiba University, <sup>2</sup>Pediatrics, Kimitsu Chuo Hospital, <sup>3</sup>Pediatrics, Chiba Kaihin Municipal Hospital, <sup>4</sup>Pediatrics, Eastern Chiba Medical Center, <sup>5</sup>Department of Allergy and Rheumatology, Chiba Children's Hospital

Conflict of interest: None

[Objectives] To clarify factors for low bone mineral density in patients with juvenile-onset autoimmune diseases using steroids [Methods] The study subjects were 70 patients with juvenile-onset autoimmune diseases who were treated with steroids in Department of Pediatrics, Chiba University Hospital from 1984 to 2014, and whose femoral neck bone mineral density was measured. They were 18 males and 52 females. Their primary diseases were SLE (24 patients), MCTD (5 patients), sJIA (18 patients), and other diseases (23 patients). The median age at which steroid therapy started was 10.7 (1.9-16.0). The median age at which their bone density was measured was 17.5 (4.5-29.8). Bisphosphonates were used in 39 patients (55.7%) for 5.4 years (0.14-14.6). We retrospectively analyzed factors for low bone mineral density and effects of bisphosphonates. [Results] The mean Z-score of their last femoral neck bone mineral density was  $-0.65 \pm 1.6$ . Forty seven percent of the subjects had low bone mineral density (Z-score  $\leq -1.0$ ), and 16 percent of the subjects had extremely low bone mineral density (Z-score  $\leq -2.0$ ). Female patients had significantly less Z-score than male patients at the age of 15 or more. The change of Z-score during bisphosphonate treatment was significantly associated with levels of ALP before the bisphosphonate treatment. [Conclusion] Patients with juvenile-onset autoimmune diseases using steroids, especially females over 15 years of age, showed low bone mineral density. As bisphosphonates had less effect in the patients with low bone turnover, the timing in which we start bisphosphonate treatment should be discussed.

#### W76-1

##### The Effects of Daily Teriparatide on the Spine and Femoral Strength Assessed by a Finite Element Analysis of Clinical Computed Tomography Scans in Rheumatoid Arthritis Patients

Kumiko Ono<sup>1</sup>, Satoru Ohashi<sup>2</sup>, Yuho Kadono<sup>1</sup>, Tetsuro Yasui<sup>1</sup>, Yasunori Omata<sup>1</sup>, Naoko Shoda<sup>1</sup>, Hiroyuki Oka<sup>3</sup>, Sakae Tanaka<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Sagami-hara Hospital, National Hospital Organization, Kanagawa, Japan, <sup>3</sup>Department of Medical Research and Management for Musculoskeletal Pain, 22nd Century Medical & Research Center, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

Conflict of interest: None

[Objectives] To confirm the effects of daily-Teriparatide (TPTD) treatment for 12 months in RA patients by CT/Finite Element Analysis (FEA). [Methods] 27 RA patients receiving TPTD were measured in two bone turnover markers (PINP and TRACP-5b) from baseline to 1, 3, 6 and 12 months, and bone mineral density (BMD) by dual x-ray absorptiometry (DXA) and spinal and femoral predicted bone strength (PBS) by CT/FEA at baseline, 6, and 12 months. [Results] Patients were aged 68.2 years. On average, PINP (baseline, 1, 3, 6 and 12 months) was 42.6, 140.4, 145.3, 162.8, 127.6 $\mu\text{g/L}$ , TRACP-5b was 422.8, 536.6, 587.8, 630.8, 590.0 mU/dL. BMD-spine (baseline, 6, 12 months) was 0.89, 0.92, 0.94 g/cm<sup>2</sup> ( $p<0.01$ ) (median change 4.4, 6.3%), BMD-femoral neck was 0.62, 0.62, 0.62 g/cm<sup>2</sup> (median change 0.8, 1.4%), PBS-spine was 3508, 3886, 407 N ( $p<0.01$ ) (mean change 13.4, 19.8%), femoral PBS-stance was 4030, 4043, 3939 N (mean change 2.0, -0.1%) and femoral PBS-fall was 1428, 1433, 1441N (mean change 1.2, 1.6%). [Conclusion] In RA patients, significant increases from baseline in BMD and PBS in the lumbar spine were seen at 6 and 12 months, while none of the values showed significant changes in the proximal femur with TPTD therapy. In the lumbar spine, PBS by CT/FEA increased more than BMD by DXA at 12 months.



## W76-2

### Daily teriparatide treatment for 2 years for osteoporosis in patients with rheumatoid arthritis - impact of concomitant oral prednisolone on effects of teriparatide-

Yuji Hirano, Shinya Hirabara, Masaaki Isono

Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan

Conflict of interest: None

[Objectives] To investigate efficacy of daily teriparatide (dTPTD) in osteoporosis (OP) in patients with rheumatoid arthritis (RA) treated with concomitant oral prednisolone (PSL). [Methods] 50 females with both OP and RA were included in this study. 2 years had passed after the initiation of dTPTD. Patients were divided into two groups, that were PSL-concomitant (PG) and PSL-nonconcomitant (NPG). Patients' characteristics, BMD in lumbar spine and total hip and change of bone turnover markers (BTMs: BAP, P1NP, NTX, TRACP-5b) were compared between two groups. [Results] Patients' characteristics: RA duration in PG was longer than that in NPG. ADL measured by class and mHAQ in PG was worse than that in NPG. LS-BMD and TH-BMD in both groups were significantly increased after initiation of dTPTD. %increase of LS-BMD at 2-year in PG and NPG were 11.0% and 14.2%, respectively. Although %increase of TH-BMD at 6m in PG (-0.5%) was significant low compared with that in NPG (3.3%), the difference was disappeared at 2-year. Although change of BTMs in PG was small compared with that in NPG, that was not significant. [Conclusion] Although dTPTD was effective in OP in RA patients, early response in TH-BMD was delayed in PG compared with NPG and oral PSL should be tapered as possible.

## W76-3

### Retrospective study on the usefulness of teriparatide for the management of steroid-induced osteoporosis in patients with collagen diseases

Hirofumi Takei, Akiko Shibata, Ryota Sakai, Kentaro Chino, Tsuneo Kondo, Ayumi Okuyama, Koichi Amano

Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University

Conflict of interest: None

[Objectives] To investigate the usefulness of teriparatide (TP) in patients with collagen diseases (CD) receiving steroids. [Methods] We retrospectively reviewed the medical records of 59 CD patients (male 9, female 50) who had received steroid therapy and were prescribed TP from April 2011 to November 2013. [Results] Mean age was 68.8 years old. RA 35, SLE 6, PM/DM 5, scleroderma 5, Sjogren 1, PMR 2, vasculitis 2, adult onset Still's disease 1, sarcoidosis 1. Fourtythree patients had a history of fragile fracture. Clinical features at the start of TP; the mean duration of steroid therapy was 129.7 months, the mean steroid (prednisolone) dose was 6 mg/day, and the mean YAM value of lumbar BMD was 73.9% (n=51). Previous therapy for osteoporosis; bisphosphonate 38 (with vitamine D, 19), SERM 4 (with vitamine D, 3), vitamine D alone 3. Mean YAM value of lumbar BMD significantly elevated to 81.7% (n=23) after one year. New vertebral fracture developed in 4 cases, but non-vertebral fractures were not seen. Five cases stopped TP due to adverse reactions (myalgia 2, arthralgia 1, boredom 2). [Conclusion] In elderly patients with CDs receiving steroids, lumbar BMD significantly elevated by treatment with TP.

## W76-4

### Effect of daily subcutaneous injection of teriparatide to sever glucocorticoid induced osteoporosis

Ikuko Tanaka<sup>1</sup>, Mari Ushikubo<sup>2</sup>, Shigenori Tamaki<sup>1</sup>, Harumi Kuda<sup>2</sup>, Keisuke Izumi<sup>2</sup>, Kumiko Akiya<sup>2</sup>, Hisaji Oshima<sup>2</sup>

<sup>1</sup>Nagoya Rheumatology Clinic, Initiative for Rheumatology and Osteoporosis, Nagoya, Japan, <sup>2</sup>Department of Connective Tissue Disease, Tokyo Medical Center

Conflict of interest: None

<Background and purpose> Bisphosphonate (Bis) does not show enough effect in protecting bone fractures in glucocorticoid induced os-

teoporosis (GIOP). The purpose of this study was to examine the protective effect of daily administration of teriparatide (dPTH) to incident fractures in severe GIOP. <Methods> Subjects were y.o., prevalent fracture rate: 32/3 (90%), average dose of glucocorticoid (G): 7.9/5.5mg/day). The primary end point in a 24 month cohort is an incident fracture on spinal X-ray, which were evaluated as Grade 1 by SQ method (Genant). Lumbar bone mineral density (BMD) was measured by DXA. <Results> 1) Serum Ca was elevated at 6 month (Mo) (p<0.05), and was lowered to the base line level. 2) NTX, TRACP5b, BAP, and P1NP increased at 6Mo (p<0.05), but did not different from the base line value after 6Mo. 3) Lumbar BMD was elevated at 12Mo and 24Mo (p<0.05). 4) The rate of incidental fracture was 14.3% at 1 year, 21.7% at 2 year, and 30.4% at 3 year. <Conclusion> dPTH is effective in increasing BMD and decreasing rate of fracture in severe GIOP, however stronger drugs are needed.

## W76-5

### Effect of once weekly dosing of teriparatide at high dose administration of steroid

Ikuko Tanaka<sup>1</sup>, Mari Ushikubo<sup>2</sup>, Shigenori Tamaki<sup>1</sup>, Harumi Kuda<sup>2</sup>, Keisuke Izumi<sup>2</sup>, Kumiko Akiya<sup>2</sup>, Hisaji Oshima<sup>2</sup>

<sup>1</sup>Nagoya Rheumatology Clinic, <sup>2</sup>Department of Connective Tissue Disease, Tokyo Medical Center

Conflict of interest: None

<Background and purpose> The dose of steroid in studies examining the effect of teriparatide to glucocorticoid induced osteoporosis (GIOP) is 5mg on average. The purpose of this study was to evaluate the effect of teriparatide on the once a week dosage (wPTH) to incident fractures at high dose of glucocorticoid (G). <Method> Subjects were 11 patients with rheumatoid arthritis who were given wPTH during high dose of G (age: 65±17y.o., average doses of G: 24.8±20.8mg/day, total dose of G: 5.7±9.1g). The primary end point in a 18 month cohort is an incident fracture on spinal X-ray, which were evaluated as Grade 1 by SQ method (Genant). Lumbar bone mineral density (BMD) was measured by DXA. <Results> 1) The lumbar BMD decreased from at the base line to at 18 week. 2) An inverse correlation was observed between the dose of G at the base line and the change of BMD (p=0.04). 3) There was a difference of G dose between the groups of increased and decreased BMD (p=0.01). 4) Two cases of incident fracture were observed within one year of wPTH medication. 5) No incident fracture was observed one year after the medication of wPTH. <Conclusion> wPTH is effective to increasing BMD and suppressing rate of the incident fracture.

## W76-6

### Influence of glucocorticoid therapy on Wnt/β-catenin signaling pathway in patients with systemic autoimmune diseases

Mai Kawazoe, Kaichi Kaneko, Kotaro Shikano, Shotaro Masuoka, Hiroshi Sato, Emiko Shindo, Natsuki Fujio, Makoto Kaburaki, Sei Muraoka, Nahoko Tanaka, Tatsuhiro Yamamoto, Natsuko Kusunoki, Tomoko Hasunuma, Shinichi Kawai

Division of Rheumatology, Department of Internal Medicine, School of Medicine, Faculty of Medicine, Toho University

Conflict of interest: None

[Objectives] Wnt/β-catenin signaling pathway plays an important role in bone formation. The influence of glucocorticoid (GC) therapy on the pathway has not been clarified yet, we then focused on serum sclerostin, Dickkopf1 (Dkk-1) and Wnt3a, inhibitors and a ligand of the pathway, to clarify the influence of GC therapy on the pathway. [Methods] 31 patients (age range 16-89 years, 18 females, 10 postmenopausal) with systemic autoimmune diseases who received initial GC therapy with prednisolone (30 to 70 mg daily) were included in this study. Regular doses of bisphosphonates were co-administered to all patients. We measured the serum levels of Wnt signaling parameters and bone turnover markers before the initiation of GC therapy and every week for 4 weeks after that. [Results] Serum levels of Wnt3a and Dkk-1 were decreased from the 1st and 2nd week after starting of GC therapy and remained at lower level. Serum sclerostin levels significantly increased from the 1st week to the 2nd in comparison to previous value, whereas no significant changes were observed from the 3rd week on. [Conclusion] We suggest

that serum sclerostin may suppress bone formation by inhibiting Wnt/ $\beta$ -catenin signaling pathway from early-phase GC therapy, and Dkk-1 may not be related with GC-induced osteoporosis.

### W77-1

#### The pathogenic mechanisms of TGF- $\beta$ /ET-1 autocrine loop in systemic sclerosis skin fibrosis

Tomoaki Higuchi, Yasushi Kawaguchi, Kae Takagi, Akiko Tochimoto, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

(Objectives) TGF- $\beta$ /ET-1 autocrine loop is thought to be a main role in various fibrotic disorders, but it remains unclear in the pathogenesis of skin fibrosis in systemic sclerosis (SSc). Our aims of this *in vitro* study is 1) to clarify how the signal transduction through TGF- $\beta$ 1 is associated with upregulation of ET-1 and 2) to examine the effects of TGF- $\beta$ 1 on the fibrotic phenotype of SSc skin fibroblasts through ET-1 and ET receptors. (Methods) Cultured SSc skin fibroblasts were incubated with TGF- $\beta$ 1 in the presence of a Smad3 inhibitor (SIS3), a JNK inhibitor (SP600125), an ETA antagonist (BQ123), an ETB antagonist (BQ788) and a dual ETA/ETB antagonist (bosentan). The profibrotic genes as *COL1A1* and *CTGF* mRNA were assessed using qPCR method. *ET-1* mRNA were also measured using qPCR and levels of ET-1 in cultured medium were calculated using an ELISA kit. (Results) SIS3 and SP600125 significantly down-regulated the expressions of *COL1A1*, *CTGF* mRNA and ET-1 production. Bosentan administration showed the additive antifibrotic effects. (Conclusion) The present study showed that ET-1 production induced by TGF- $\beta$ 1 was both Smad and JNK signaling pathway-dependent in SSc skin fibroblasts. Furthermore, dual ETA/ETB blockade may be indispensable to improvement of skin fibrosis in SSc.

### W77-2

#### Predictors of mortality in patients with pulmonary arterial hypertension (PAH) associated with connective tissue disease (CTD)

Hiroaki Tanaka<sup>1</sup>, Satoshi Kubo<sup>1</sup>, Kazuhisa Nakano<sup>1</sup>, Shingo Nakayamada<sup>1</sup>, Shintaro Hirata<sup>1</sup>, Shunsuke Fukuyo<sup>1</sup>, Ippei Miyagawa<sup>1</sup>, Kazuyoshi Saito<sup>1</sup>, Kunihiro Yamaoka<sup>2</sup>, Yoshiya Tanaka<sup>1</sup>

<sup>1</sup>The First Department of Internal Medicine, University of Occupational and Environment Health, Kitakyusyu, Japan, <sup>2</sup>Division of Rheumatology, Clinical Immunology, Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan

Conflict of interest: None

[Objectives] To investigate the clinical features and predictors of mortality in patients with PAH associated with CTD [Method] 58 patients with CTD-PAH were enrolled in this study between 2005 and 2012. The cumulative survival rate and NYHA functional classification (FC) changes in 5 years were collected by Kaplan-Meier and LOCF method. [Results] Mean age was 62 years and 88% of patients were female at the baseline. The underlying CTD include SLE (19%), MCTD (16%), and SSc (43%). The 5-years cumulative survival rate was 79%. NYHA-FC at baseline was significantly different between survivors and fatal case ( $P < 0.01$ ). Survival rate was significantly higher in the patients with NYHA-FC I/II (89%) than NYHA-FC III/IV (60%) at diagnosis. Comparison among the three groups (NYHA-FC improved, unchanged, or worse) revealed no differences in NYHA-FC at diagnosis, serum BNP and treatment regimens, while there were significantly different in underlying CTD. 54% of the patients with SLE improved NYHA-FC, whereas only just 8% of the patients with SSc improved NYHA-FC. [Conclusion] Early detection of PAH is important for good outcome. Treatment response was significantly different between SLE and SSc, suggesting that treatment strategy should be considered according to underlying CTD.

### W77-3

#### Association of BTB and CNS homology 2 (*BACH2*) gene polymorphism with systemic sclerosis (SSc) in Japanese population

Kae Takagi<sup>1</sup>, Yasushi Kawaguchi<sup>2</sup>, Manabu Kawamoto<sup>2</sup>, Yuko Ota<sup>2</sup>, Tomoaki Higuchi<sup>2</sup>, Chikako Fukasawa<sup>2</sup>, Akiko Tochimoto<sup>2</sup>, Hisae Ichida<sup>2</sup>, Hisashi Yamanaka<sup>2</sup>

<sup>1</sup>Department of Medicine, Tokyo Women's Medical University Medical Center East, Tokyo, Japan, <sup>2</sup>Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Purpose] *BACH2* play a crucial role in somatic hypermutation, class switch recombination, and plasma cell differentiation immunosenescence and cytokine production. Single nucleotide polymorphisms (SNPs) of *BACH2* gene are associated with numerous autoimmune and allergic diseases including asthma, Crohn's disease, coeliac disease, multiple sclerosis and type 1 diabetes. *Bach2* knock out mice exhibits autoimmune phenotype with reduced regulatory T cells. These observations suggest a critical role of *BACH2* in autoimmune disease susceptibility. In this report, we have explored the association of *BACH2* SNPs and SSc. [Methods] Case control study was performed in 256 Japanese SSc patients and healthy controls. Four SNPs (rs11755527, rs3757247, rs9344996, rs2474619) of *BACH2* gene were genotyped using the Taqman assay. [Results] *BACH2* gene rs1175552 was significantly associated with SSc development. Odd ratio (OR) 1.43 (95% CI 1.08-1.90,  $p = 0.01$ ). Association between anti-scl-70 antibody with rs11755527, Reynaud's-phenomenon with rs3757247 and rs2474619, digestive complication with rs9344996, pitting scar with rs2474619, was observed respectively ( $p < 0.05$ ). [Conclusions] This study provides robust evidence for an association of SSc susceptibility with *BACH2* polymorphism in the Japanese population.

### W77-4

#### The slope of estimated sPAP/CO as well as maxTRPG by exercise stress echocardiography might be useful to evaluate the subclinical disorders of pulmonary vascular system in systemic sclerosis

Yoshinobu Koyama, Toshie Higuchi

Department of Rheumatology, Center for Autoimmune Diseases, Japanese Red Cross Okayama Hospital

Conflict of interest: Yes

[Objectives] To detect the subclinical disorders of pulmonary vascular system in systemic sclerosis (SSc). [Methods] The 30 patients categorized class 1 by NYHA and WHO functional classification with 1) elevated BNP or 2) Raynaud symptoms or 3) sclerodactylia, were included. The slope of estimated systolic pulmonary artery pressure (sPAP)/cardiac output (CO) and the maximum tricuspid regurgitation pressure gradient (maxTRPG) were calculated with Master's two-step stress echocardiography. SSc patients including overlap syndrome ( $n = 19$ ) were compared with non-SSc patients ( $n = 11$ ). Moreover, seven of cases were evaluated by right heart catheterization (RHC). [Results] No significant difference was detected in serum BNP or resting TRPG between SSc and non-SSc group. On the other hand, max TRPG ( $40.0 \pm 12.2$  vs  $25.8 \pm 7.37$  mmHg) or the slope of estimated sPAP/CO ( $6.83 \pm 3.98$  vs  $3.32 \pm 1.93$  mmHg·min/L) was significantly high in SSc group ( $p < 0.01$ ). The slope of estimated sPAP/CO was significantly correlated with mean PAP/CO measured by RHC ( $r = 0.57$ ,  $p < 0.01$ ). [Conclusion] Although serum BNP or resting TRPG was not sensitive enough to evaluate subclinical disorders of pulmonary vascular system in SSc, the estimated sPAP/CO as well as max-TRPG might be useful to detect it.

### W77-5

#### Assessment of the efficacy of nailfold videocapillaroscopy in diagnosing systemic sclerosis

Yuki Ichimura, Naoko Konda, Tomoaki Higuchi, Naohiro Sugitani, Rina Furukusa, Eri Sugano, Kumiko Saka, Hirokazu Nishina, Tomoya Harada, Yuko Okamoto, Masanori Hanaoka, Daisuke Hoshi, Tsuyoshi Kobashigawa, Hisae Ichida, Yasuhiro Katsumata, Yasushi Kawaguchi, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo,

Japan

Conflict of interest: None

[Objectives] Capillary abnormalities observed by nailfold videocapillaroscopy (NVC) are useful to diagnose systemic sclerosis (SSc). However, there are few reports about NVC in Japan. We aimed to estimate the efficacy of NVC in the diagnosis and the association with clinical features in patients with SSc. [Methods] NVC findings were collected from 28 adult Japanese patients with connective tissue diseases including 14 patients with SSc. Ten fingers of each patient were evaluated by NVC to classify and score the semi-quantitative rating. The associations between clinical manifestations and NVC patterns were assessed. [Results] An average of 7.0 fingers of ten was observed properly. Patients with SSc tended to have irregular patterns more frequently than non-SSc patients, especially loss of capillary. Unexpectedly, there were no differences between NVC patterns and clinical manifestations in this study. [Conclusion] NVC may be a valuable tool in diagnosing SSc even in Japanese patients, because capillary abnormalities were more frequently observed in SSc. As previously reported, irregular NVC patterns were also observed in patients other than SSc. Further investigation of NVC patterns is warranted to assess their efficacy in early diagnosis of SSc among Japanese population.

### W77-6

#### **Relationship of the nailfold videocapillaroscopy (NVC) stage and clinical manifestations in systemic sclerosis**

Shoko Kodama, Tomoya Miyamura, Makiko Higuchi, Yu Kaku, Masataka Nakamura, Soichiro Takahama, Rumi Minami, Masahiro Yamamoto, Eiichi Suematsu  
Department of Internal Medicine and Rheumatology, Clinical Research Institute, National Hospital Organization, Kyushu Medical Center, Fukuoka, Japan

Conflict of interest: None

Objective Since the classification criteria of systemic sclerosis (SSc) revised, The nailfold capillary changes (NFCC) have had significant meaning on diagnosis of SSc. We investigated the relationships of NFCC observed nailfold videocapillaroscopy (NVC) and clinical manifestations in SSc. Methods Eleven patients (mean age 64.8 years old) enrolled in this study. We analyzed the NFCC stage by NVC, clinical manifestations, autoantibody of SSc and organ involvement. Results Diffuse type patients are six in Eleven patients. The number of early stage, active stage and late stage of NVC stage were two, three and seven, respectively. The proportion of digit ulcers (DU) was larger at active stage. Anti-Scl70 antibodies were higher than other autoantibodies at late stage. Autonomic nervous system dysfunctions (ANS) had a high prevalence at late stage (85.7%) compared with active stage (33.3%). Morbidity of pulmonary hypertension (PH) was 50% at active stage compared with late stage (14.2%). Conclusions Our data indicated DU and PH at active stage were high prevalence, and the population of cardiac involvement caused by ANS were higher at late stage. NFCC observed in NVC are important findings not only at the time of diagnosis, but also at the evaluations of SSc complications.

### W78-1

#### **Analysis of pulmonary artery hypertension with systemic sclerosis using ultrasound-cardiography**

Yu Matsueda, Sumiaki Tanaka, Mei Tani, Kako Kodama, Nobuhiro Sho, Eisuke Ogawa, Yoshiyuki Arinuma, Tatsuhiko Wada, Tatsuo Nagai, Shunsei Hirohata  
Department of Rheumatology and Infectious Diseases Kitasato University School of Medicine, Kanagawa, Japan

Conflict of interest: None

Objectives: Survival in patients of pulmonary artery hypertension (PAH) with systemic sclerosis (SSc) is poor. We studied to clarify the complicated pathophysiology of PAH with SSc. Methods: We selected 202 patients with SSc and 420 patients with another connective tissue diseases (CTD) who received therapy in our hospital from 2001 until

2014, and analyzed 4436 reports of ultrasound-cardiography obtained from these patients. We divided it into SSc group and non-SSc group and compared with pulmonary artery pressure (PAP), right atrium area size (RAAs), left atria area size (LAAs) in the presence or absence of PAH. Results: Of the 117 patients with PAH, 52 patients belonged SSc group. PAH patients were treated according to a goal-oriented therapeutic strategy using PAH-specific drugs. In both groups, PAP and RAAs showed significantly higher value in patients with PAH than in patients without PAH. In SSc group, LAAs showed significantly larger in patients with PAH than in patients without PAH (20.45 cm<sup>2</sup> vs. 18.32 cm<sup>2</sup>, p=0.0164), but not in non-SSc group. Conclusion: Our results demonstrate that LAAs incorporate left heart disease and may relate with poor survival in patients of PAH with SSc. We indicate that the evaluation of LAAs is useful for diagnosis and treatment PAH.

### W78-2

#### **Serum CD146 levels of our patients with Systemic sclerosis**

Tomoko Ito<sup>1</sup>, Naoto Tamura<sup>1</sup>, Sayuri Okuda<sup>2</sup>, Kurisu Tada<sup>1</sup>, Ken Yamaji<sup>1</sup>, Kazunori Kato<sup>2</sup>, Yoshinari Takasaki<sup>1</sup>  
<sup>1</sup>Juntendo University School of Medicine, Tokyo, Japan, <sup>2</sup>Department of Biomedical Engineering, Toyo University

Conflict of interest: None

[Objectives] CD146 is a transmembrane glycoprotein belong to Ig-superfamily and acts as adhesion molecule for the maintenance of cell monolayer. Human endothelial cells, activated fibroblasts and Th17 cells express CD146 that related in the angiogenesis, fibrosis and inflammation. We established sandwich ELISA for soluble CD146 (sCD146). The aim of this study is to determine the levels of sCD146 in the serum of patients with Systemic sclerosis (SSc), and to examine the relationship between the levels of sCD146 and the clinical variables. [Methods] Blood samples were drawn from patients fulfilling criteria for SSc proposed by the 2013 Classification Criteria for SSc (ACR/EULAR) Levels of sCD146 were quantified in 23 serum samples from patients with SSc by ELISA and compared with those of 14 healthy subjects. The titers of KL-6 for each patient were determined simultaneously. [Results] Levels of sCD146 were significantly higher in patients with SSc (11.9 ng/ml) than in the healthy subjects (5.2 ng/ml; p<0.01). However, no correlation between sCD146 and KL-6 titer was observed. [Conclusion] We identified the presence of sCD146 in SSc serum. Correlation between sCD146 and the clinical variables such as pulmonary hypertension and fibrosis will be determined.

### W78-3

#### **The impact of therapeutic intervention for systemic sclerosis-associated interstitial lung disease**

Miki Takata, Ryota Okazaki, Akira Yamasaki, Eiji Shimizu  
Division of Medical Oncology and Molecular Respiriology Tottori University Faculty of Medicine, Tottori, Japan

Conflict of interest: None

[Objectives] Cyclophosphamide is reported to be effective for the treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD), however such benefit disappears after cessation of therapy. Here we investigated the relationship between therapeutic intervention and prognosis. [Methods] Between April 2004 and September 2014, SSc patient with IP were enrolled in this study. The parameters including autoantibodies, HRCT pattern, presence of prednisone or other immunosuppressive agents, pulmonary function, annual rate of decline in %VC and %DL<sub>CO</sub>, and outcome were investigated retrospectively. [Results] Among 42 patients (4 men and 38 women; 56.5 ± 14.8 years of age), 8 (19%) were positive for anti-centromere antibody and 20 (47.6%) were positive for anti-Scl-70 antibody. In HRCT, 32 cases (76.2%) were NSIP/P, 6 (14.3%) were UIP/P, 1 (2.4%) was DAD/P. 26 cases (61.9%) were received therapy. There was no significant difference in annual rate of decline in %VC and %DL<sub>CO</sub> between treated group and non-treated group. Deaths during clinical course were 6 cases in treated group and 1 case in non-treated group. [Conclusion] Therapeutic intervention for SSc-ILD didn't decrease deterioration in pulmonary function. Clinical indication of therapy should be determined carefully.

## W78-4

### A parallel-group comparison study of tocilizumab therapy in patients with systemic sclerosis

Yoshihito Shima<sup>1</sup>, Masataka Kuwana<sup>2</sup>, Yasushi Kawaguchi<sup>3</sup>

<sup>1</sup>Osaka University Graduate School of Medicine, Allergy and Rheumatic Diseases, <sup>2</sup>Department of Allergy and Collagen Disease Science, Nippon Medical School, <sup>3</sup>Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: None

[Objectives] To understand the efficacies of anti-interleukin-6 receptor antibody (tocilizumab [TCZ]) in patients with systemic sclerosis, we established an open-label, parallel-group comparison study. [Methods] Patients were recruited from Keio University Hospital, Tokyo Women's Medical University Hospital, and Osaka University Hospital and were randomly divided into two groups: the TCZ add-on group (TCZ group) and the conventional therapy group (Conv group). In TCZ group, 8 mg/kg/month of TCZ was administered for six months. The modified Rodnan total skin score (mRTSS) was used to compare the efficacy. [Results] Six patients were enrolled in TCZ group and five patients were enrolled in Conv group. The average mRTSS in TCZ group was 22.5 and that in Conv group was 26.8. Two patients in TCZ group were excluded on their own insistence and event of fever. At the end of six months, the average mRTSS change in TCZ group was larger (6.3 points) than that in Conv group (3.4 points), but the variation was substantially large to constitute a significant difference. [Conclusion] Although a significant difference was not observed, some patients in TCZ group showed decrease in mRTSS during the administration period.

## W78-5

### Retrospective study about the predictive clinical tests to detect borderline pulmonary hypertension related to systemic sclerosis

Yoshihide Ichise<sup>1</sup>, Goh Tsuji<sup>1</sup>, Kyosuke Abe<sup>1</sup>, Mayuko Izumi<sup>1</sup>, Ai Muta<sup>1</sup>, Ryosuke Umeda<sup>1</sup>, Sho Sendo<sup>2</sup>, Yuko Uemura<sup>3</sup>, Shunichi Kumagai<sup>1</sup>

<sup>1</sup>Department of Rheumatic Disease Shinko Hospital, Hyogo, Japan, <sup>2</sup>Department of Rheumatology and Clinical Immunology Kobe University Hospital, Hyogo, Japan, <sup>3</sup>Institute of Medicine Research, Shinko Hospital, Hyogo, Japan

Conflict of interest: None

[Background] The prognosis of pulmonary hypertension (PH) related to systemic sclerosis (SSc) is quite poor. Borderline PH is seemed to precede overt PH in SSc. Screening examinations for overt PH, for example "estimated right ventricle systolic pressure in transthoracic echocardiography (sPAP) >40mmHg", or "%DLco <50% in pulmonary function test", are not enough to distinguish borderline PH from normal. [Objectives] To clarify predictive examinations to detect borderline PH related to SSc. [Methods] 47 patients of SSc underwent right heart catheterization studies. We analyzed them about backgrounds and the results of clinical tests retrospectively and defined ideal cut-off levels to some significant tests. [Results] Three of all patients whose pulmonary capillary wedge pressure was more than 15mmHg were excluded. Eight of 44 had a mean PAP (mPAP) more than 21mmHg (2 patients had a mPAP  $\geq$ 25mmHg, overt PH) and other 36 patients had a normal mPAP. %DLco and sPAP are significantly related to mPAP. The appropriate cut-off values are 70% of %DLco and 35mmHg of sPAP. Sensitivity and specificity are 85.7% (62.5%) and 80% (86.1%) about %DLCO and (sPAP). [Conclusion] We may set up cut-off levels more strictly to pick up borderline PH in SSc than overt PH.

## W78-6

### Clinico-pathological analysis of renal involvement in the patients with anti-RNP antibody

Toshiharu Ueno<sup>1</sup>, Ryo Hazue<sup>1</sup>, Akinari Sekine<sup>1</sup>, Koki Mise<sup>1</sup>, Masahiro Kawada<sup>1</sup>, Keiichi Sumida<sup>1</sup>, Rikako Hiramatsu<sup>1</sup>, Eiko Hasegawa<sup>1</sup>, Noriko Hayami<sup>1</sup>, Tatsuya Suwabe<sup>1</sup>, Junichi Hoshino<sup>1</sup>, Naoki Sawa<sup>1</sup>, Kenmei Takaichi<sup>1</sup>, Yoshifumi Ubara<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Toranomon Hospital, <sup>2</sup>Department of Pathology, Toranomon Hospital

Conflict of interest: None

[Objectives] To investigate the clinical and pathological background of the patients with anti-RNP antibody. [Methods] Divide 31 patients with anti-RNP antibody into four groups; low dsDNA and negative Sm antibodies, low dsDNA and positive for Sm antibodies, high dsDNA and negative Sm antibodies, and High dsDNA and positive Sm antibodies. [Results] Despite of the value of dsDNA antibody, Sm-positive patients indicated low complement. Low dsDNA and negative Sm antibody demonstrated significantly higher proteinuria. [Conclusion] Among the patient with anti-RNP antibody positive patients, low dsDNA and negative Sm antibody may associated with specific pathophysiology.

## W79-1

### Changes of glomerular podocyte markers and calcineurin expressions in lupus nephritis

Ayako Wakamatsu<sup>1</sup>, Yoko Wada<sup>1</sup>, Chinatsu Takai<sup>1</sup>, Yukiko Nozawa<sup>1</sup>, Hiroe Sato<sup>1</sup>, Takeshi Nakatsue<sup>1</sup>, Takeshi Kuroda<sup>2</sup>, Masaaki Nakano<sup>3</sup>, Ichiei Narita<sup>1</sup>

<sup>1</sup>Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, <sup>2</sup>Niigata University Health Administration Center, Niigata, Japan, <sup>3</sup>School of Health Sciences Faculty of Medicine, Niigata, Japan

Conflict of interest: None

[Background] Calcineurin inhibitor is known to have a non-immunological anti-proteinuric effect by directly affecting slit diaphragm of podocyte in lupus nephritis (LN). [Objectives] To analyze the glomerular expression of slit diaphragm markers and CN in LN. [Methods] Eight patients with systemic lupus erythematosus (SLE) who underwent percutaneous renal biopsy, were recruited. Their biopsy specimens were classified as class I, II, IV, and V (n=2 in each class), according to the ISN-RPS classification of LN. The glomerular expression of podocin, ZO-1, CN, and podocalyxin, were analyzed by immunofluorescence. [Results] The staining pattern of podocin and CN dramatically changed from linear to coarse granular in all specimens, compared to normal control. In addition, the intensity was significantly reduced in those with class IV and V. The staining pattern of ZO-1 also shifted to coarse granular in all classes, whereas the intensity was not decreased. The staining pattern and intensity of podocalyxin were not changed in all classes of LN. [Conclusion] There were significant changes of expressions for podocin, ZO-1, and CN, even in class I LN. These finding suggested dysfunction of podocyte and especially in slit diaphragm, might be involved even in early stage of LN.

## W79-2

### Predicting histologic features in lupus nephritis using urinary podocyte marker

Daisuke Ikuma<sup>1</sup>, Hiroshi Kajiyama<sup>1</sup>, Keiju Hiromura<sup>2</sup>, Hidekazu Ikeuchi<sup>2</sup>, Kojiro Sato<sup>1</sup>, Yuji Akiyama<sup>1</sup>, Yoshihisa Nojima<sup>2</sup>, Toshihide Mimura<sup>1</sup>

<sup>1</sup>Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Saitama, Japan, <sup>2</sup>Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine, Gunma, Japan

Conflict of interest: None

Objectives: We tested whether histologic features in lupus nephritis (LN) were predicted by using numbers of urinary podocyte (U-Pod/Cr) and concentrations of urinary podocalyxin (U-PCX). Methods: From January 2011 to July 2014, urine samples before initiation of therapy were obtained from 41 active LN patients. U-Pod/Cr was obtained from PCX-positive cell numbers in the sediments divided by the urine creatinine. U-PCX was measured by sandwich ELISA. Histologic Activity and Chronicity Indices (Austin, 1984) were scored by examiner-blinded methods. Results: U-Pod was higher in patients with ISN/RPS class IV than in patients without the condition (P<0.05), which was not seen in U-PCX. There was positive correlation between glomerular Activity Index (gAI) and U-Pod/Cr ( $r=0.5432$ , P<0.01). There was no significant correlation between gAI and U-PCX. Multiple linear regression analysis showed significant correlations between U-Pod/Cr and cellular crescent

(CC,  $P < 0.05$ ), U-PCX and CC ( $P < 0.01$ ), U-PCX and segmental/global glomerulosclerosis (GS,  $P < 0.01$ ). ROC analysis showed U-Pod/Cr ( $> 7.418$  cells/mgCr) could predict CC (sensitivity 61.11%, specificity 94.70%) in LN patients. Conclusions: U-Pod/Cr may be useful for predicting the presence of CC. U-PCX may be affected by GS and CC.

### W79-3

#### The associations between pathological findings and the rate of eGFR change in lupus nephritis

Daiga Kishimoto, Yumiko Sugiyama, Naomi Tsuchida, Yosuke Kunishita, Reikou Kamiyama, Kaoru Minegishi, Maasa Hama, Ryusuke Yoshimi, Yohei Kirino, Atsuhisa Ueda, Yoshiaki Ishigatsubo  
Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine

Conflict of interest: None

[Objectives] A 30% reduction of eGFR over 2 years is suggested as an alternative end point for CKD. We evaluated usefulness of this in lupus nephritis (LN) patients and pathological findings affect eGFR or not. [Methods] We extracted 46 LN patients (mean age 33.5 y.o, female  $n = 43$ ). And we investigate patients who got a 30% eGFR reduction over 2 years. We analyzed associations between rate of eGFR change and existence of some pathological findings. [Results] The RBx samples were classified into Class I/II/III/IV/V (1/5/15/22/3). Proliferative nephritis, membranous nephritis, tubulointerstitial infiltration, thrombi, glomerular sclerosis, and crescent were found in 87.0%, 28.3%, 56.5%, 19.6%, 58.7%, and 23.9% of the specimens, respectively. The 69.6% and 76.1% patients were conducted mPSL pulse therapy and IVCY, respectively. No patients got ESRD but a 30% reduction of eGFR over 2 years was founded in 3 cases. Existence of these pathological findings did not give significant difference about rate of eGFR change. [Conclusion] A 30% reduction of eGFR over 2 years was founded in 3 of 46 cases. Whether this alternative end point associate with ESRD and HD or not need more analysis by using large database. And to investigate pathological findings which affect eGFR, further studies are needed.

### W79-4

#### Predictors of histological remission of lupus nephritis

Hidetoshi Kagawa<sup>1</sup>, Tsutomu Hiromasa<sup>1</sup>, Ryutarō Yamanaka<sup>1</sup>, Reika Takemoto<sup>1</sup>, Ken-ei Sada<sup>2</sup>, Hirofumi Makino<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Himeji Red Cross Hospital, Himeji, Japan, <sup>2</sup>Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

Conflict of interest: None

[Objectives] To determine the predictors of histological remission (HR) of lupus nephritis (LN). [Methods] Six LN patients (mean age 43.3 years) in proteinuria remission ( $< 0.2$  g/day) underwent repeat renal biopsy. All had been treated with a combination of corticosteroids and two immunosuppressive agents (mizoribine and tacrolimus). We examined the relationship between findings on renal biopsy specimens and clinical indices (severity of proteinuria levels and albuminuria, renal function, urinary sediment, serum C3 concentrations, anti-ds-DNA antibody titers, and various criteria for clinical remission) to determine the predictors of HR of LN. HR was defined as C3 and C1q negativity by fluorescent antibody methods. [Results] Repeat renal biopsy was performed at a mean treatment duration of 32 months. Four of the six patients (67%) were in HR. Compared with those not in HR, those with HR had normal serological indicators and urinary sediment; however, there was no difference between these groups in severity of proteinuria and albuminuria and renal function. Of the various criteria for clinical remission, systemic lupus erythematosus disease activity index remission was the most useful. [Conclusion] The treatment goal of LN should be normalization of both serological and renal indicators.

### W79-5

#### Analysis of CD26<sup>+</sup> T cell subsets in systemic lupus erythematosus patients as a novel biomarker of pathophysiology or disease activity

Ryo Hatano<sup>1,2</sup>, Kei Ohnuma<sup>1</sup>, Tomonori Ishii<sup>3</sup>, Satoshi Iwata<sup>1</sup>, Ko Okumura<sup>2</sup>, Iwao Sekigawa<sup>4</sup>, Chikao Morimoto<sup>1</sup>

<sup>1</sup>Department of Therapy Development and Innovation for Immune Disorders and Cancers, Graduate School of Medicine, Juntendo University, Tokyo, Japan, <sup>2</sup>Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, Tokyo, Japan, <sup>3</sup>Department of Hematology and Rheumatology, Tohoku University Graduate School of Medicine, Sendai, Japan, <sup>4</sup>Department of Internal Medicine and Rheumatology, Juntendo University Urayasu Hospital, Urayasu, Japan

Conflict of interest: None

[Objectives] T cell costimulatory molecule CD26 is up-regulated following T cell activation, and the increased number of CD26<sup>+</sup> T cells has been detected in patients with autoimmune diseases including RA. Since the role of CD26 in the pathogenesis of SLE still remains to be elucidated, our objective is to examine the expression and function of CD26 in T cells of SLE patients. [Methods] Human CD4<sup>+</sup> or CD8<sup>+</sup> T cells were purified from PBMCs of 30 SLE patients or 30 healthy adult volunteers. The expression pattern of CD26 and the phenotypes of CD26 positive or negative subsets were extensively examined by flow cytometry. [Results] CD4<sup>+</sup>CD26<sup>neg</sup> T cells were markedly increased in SLE patients compared with healthy controls. In contrast, the occurrence of CD8<sup>+</sup>CD26<sup>+</sup>CD28<sup>neg</sup> T cells was observed in active SLE patients, while this population was never observed in healthy controls. Furthermore, this CD8<sup>+</sup> T cell subset seemed to be a terminally differentiated effector cells with high expression of both perforin and granzyme B, suggesting that the appearance of these populations may be associated with the SLE disease activity or treatment protocol. [Conclusion] Our data show that the expression pattern of CD26 on peripheral blood T cells of SLE patients is quite different from healthy controls.

### W79-6

#### The role of TGF- $\beta$ 3 in the pathogenesis of murine lupus

Toshihiko Komai, Tomohisa Okamura, Yukiko Iwasaki, Kaoru Morita, Mariko Inoue, Keishi Fujio, Kazuhiko Yamamoto  
Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Conflict of interest: None

[Objectives] Our previously identified TGF- $\beta$ 3-producing CD4<sup>+</sup>CD25<sup>+</sup>LAG3<sup>+</sup> regulatory T cells (LAG3<sup>+</sup> Tregs), which do not produce TGF- $\beta$ 1, control humoral immunity through TGF- $\beta$ 3 production. We have investigated the role of TGF- $\beta$ 3 in the pathogenesis of murine lupus through comparative analysis with TGF- $\beta$ 1. [Methods] Lupus-prone MRL/lpr mice were injected with either plasmid pCAGGS vector, pCAGGS-Tgfb1 vector or pCAGGS-Tgfb3 vector. Comparative analyses of chronological proteinuria, spleen weights, serum anti-dsDNA antibody titers, cytological changes by flow cytometry, and pathological changes were conducted. [Results] MRL/lpr mice that had received pCAGGS-Tgfb3 vector, but not pCAGGS-Tgfb1 vector, showed less splenomegaly, reduced proteinuria with improvement of renal pathology, and reduced autoantibody production. Cytologically, follicular helper T cells and B cell developments were also suppressed in the MRL/lpr mice treated with pCAGGS-Tgfb3 vector. [Conclusion] TGF- $\beta$ 3 significantly improved lupus pathogenesis of MRL/lpr mice. These findings suggest that TGF- $\beta$ 3 might have an advantage over TGF- $\beta$ 1 to regulate autoantibody-mediated autoimmune diseases, such as systemic lupus erythematosus.

### W80-1

#### Association of serum C5a with neuropsychiatric syndromes in patients with systemic lupus erythematosus

Yuko Sakuma, Yoshiyuki Arinuma, Tatsuo Nagai, Takayuki Hoshiyama, Shunsei Hirohata

Department of Rheumatology and Infectious Diseases Kitasato University School of Medicine

Conflict of interest: None

[Objectives] In patients with systemic lupus erythematosus (SLE), the breakdown of blood brain barrier (BBB) integrity is associated with the development of neuropsychiatric manifestations (NPSLE), especially diffuse psychiatric/neuropsychological syndromes (diffuse NPSLE), involving inflow of autoantibodies from systemic circulation into central nervous system (CNS). C5a has been reported as an important factor which can cause BBB damage. The present study was undertaken to examine levels of C5a in sera obtained from various types of NPSLE patients. [Methods] We examined serum C5a by ELISA in 39 patients with SLE (12 with diffuse NPSLE, 9 with focal NPSLE and 18 without NPSLE) and 20 healthy controls (HC). Of the diffuse NPSLE patients, 9 had acute confusional state (ACS). [Results] Serum levels of C5a from SLE patients were significantly higher than those from HC. Furthermore, serum C5a levels from diffuse NPSLE patients with ACS were significantly elevated than those from SLE patients without NPSLE, and were higher than those from diffuse NPSLE patients without ACS or from focal NPSLE patients. [Conclusions] These results indicate that serum C5a might be associated with the development of diffuse NPSLE with ACS.

### W80-2

#### Evaluating clinical features of neuropsychiatric lesion and their therapeutic response in SLE patients

Maasa Hama, Yumiko Sugiyama, Naomi Tsuchida, Yosuke Kunishita, Daiga Kishimoto, Reikou Kamiyama, Kaoru Minegishi, Ryusuke Yoshimi, Yohei Kirino, Atsuhisa Ueda, Yoshiaki Ishigatsubo  
Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Conflict of interest: None

[Objectives] Establishing precise diagnosis algorithm and treatment strategy for NPSLE remains a challenge. We investigated the prevalence, character, and therapeutic response of neuropsychiatric lesion among SLE patients. [Methods] We prospectively analyzed the clinical features and findings of CNS examinations of 25 SLE patients who were planned to strengthen immunosuppressant therapy. [Results] Ten patients were diagnosed with having ACR-defined NPSLE (aseptic meningitis 2, acute confusional state 2, anxiety disorder 2, cognitive disorder 3, mood disorder 2). The clinical features except NP and autoantibody profile were similar between NP and non-NP group except 4 complicated with APS belonged to NP group. At baseline, though pleocytosis was seen in only 3 NP patients and NP group showed having lower IQ, increased protein and high IgG index of CSF, cerebral hypoperfusion in SPECT, and slow wave in EEG were confirmed even among non-NP group without significant difference to NP group. Perfusion in SPECT was restored in 10 of 15 patients after treatment, whereas 4 experienced further lowering of perfusion associated with clinical deterioration. [Conclusion] SLE patients have subclinical inflammation and disability of NP. Appropriate assessment and intervention for NP are important.

### W80-3

#### Today's situation of treatment selection of SLE patients of our institute

Shigeki Makino, Takeshi Shoda, Takuya Kotani, Shuzo Yoshida, Tohru Takeuchi, Toshiaki Hanafusa  
1st Department of Internal Medicine, Osaka Medical College, Osaka, Japan

Conflict of interest: Yes

[Objectives] There is an opinion that combination therapy of immunosuppressants (IS) is useful in SLE treatment. We intensively use IS. So, we aim to know today's status of IS use and management conditions of SLE patients of our institute. [Methods] We reviewed clinical data concerning treatment and clinical indicators of our SLE patients in September 2014. [Results] Total SLE patients were 324 (35 males). Patients prescribed with 2 or more IS are 72 (22%). Patients prescribed with 1 IS are 155 (48%). Patients prescribed with corticosteroid only are 73 (23%). Patients prescribed with neither corticosteroid nor IS are 24 (7%). Among immunosuppressants used, tacrolimus are prescribed to 143 (44%) patients, azathiopurin are prescribed to 86 (27%) patients, mizoribin are prescribed to 55 (17%) patients. Only 5 patients (2%) are in dialysis

state. Only 21 patients have proteinuria (7%). Patients with positive anti ds-DNA are 54 (17%). Patients with low C3 are 43 (13%). [Conclusion] Intensive use of IS may be useful for treatment of SLE patients.

### W80-4

#### Three cases of thrombotic microangiopathy (TMA) complicated with SLE

Kazuhito Fukuoka, Tomohiro Maesono, Noriko Ikegaya, Satoshi Hayakawa, Hideki Shimizu, Sayaka Miyazawa, Takayuki Takahashi, Miho Karube, Yoshinori Komagata, Shinya Kaname, Yoshihiro Arimura  
1st Internal Medicine, division of Rheumatology and Nephrology, Kyorin University School of Medicine

Conflict of interest: None

[Objectives] We attempt to clarify the characteristics of TMA's in SLE cases, furthermore elucidate the pathophysiology of these situation. [Methods] We analyzed the data and clinical course of three SLE cases complicated with TMA retrospectively, then clarify the characteristics of TMA in SLE. [Results] Case 1 was a thrombotic microangiopathy, who showed low serum ADAMTS 13 activity extremely, and onset during high disease activity of SLE, then noted good response by glucocorticoid therapy. Case 2 was an atypical HUS, who showed refractory anemia with moderately decrease of ADAMTS 13. Case 3 onset TMA at the phase of end-stage kidney disease due to lupus nephritis, while the disease activity of SLE has already been burned out. She was noted mild ADAMTS13 activity and absent of ADAMTS13 inhibitor. However plasma exchange and high amount of glucocorticoid therapy was done, these therapies showed little effects on her TMA. TMA in this case was suggested to atypical HUS due to the deficiency of H factor which was complement regulator, by the hemolytic tests using sheep red blood cells. [Conclusion] TMA was sometimes found in SLE, which showed diverse characteristics, even if the disturbance of complement activity regulation might be exist.

### W80-5

#### Characteristics of male systemic lupus erythematosus patients in our hospital

Harumi Shirai<sup>1</sup>, Hirofumi Shoda<sup>1</sup>, Satomi Kobayashi<sup>2</sup>, Keigo Setoguchi<sup>2</sup>, Keishi Fujio<sup>1</sup>, Kazuhiko Yamamoto<sup>1</sup>  
<sup>1</sup>The University of Tokyo Hospital, Tokyo, Japan, <sup>2</sup>Tokyo Metropolitan Cancer and Infectious Diseases Center

Conflict of interest: None

[Objectives] SLE is an autoimmune disease and predominantly affects females in their childbearing age. In general, male SLE patient is rare and a female-to-male ratio is 10:1. Although there were some reports about the characteristics of male SLE patients in European countries, more studies were required especially in Japanese patients. We reported some characteristics of male SLE patients in our hospital last year. Here, we collected additional cases to compare the female SLE to male SLE patients. [Methods] We retrospectively researched SLE patients who were newly diagnosed from January 2006 through August 2014 in our hospital. We checked ages at diagnosis, blood cell counts, complements, clinical features, SLEDAI, treatment, and so on. These data were obtained from their medical records. [Results] Thirty-seven SLE patients were included, who consisted of 8 male (21.6%) and 29 (78.4%) females. In male SLE patients, significantly higher C4, lower rate of thrombocytopenia, SLEDAI and older age at diagnosis were observed. In addition, lower tendencies of skin rash and nephritis were observed in male SLE patients. [Conclusion] Male SLE patients in our hospital have some significant characteristics in comparison with female SLE patients, especially older age and lower SLEDAI scores.

### W80-6

#### Investigation of systemic lupus erythematosus patients with ascites

Takayuki Kon, Takayoshi Tsukahara, Yoshiyuki Abe, Seiichiro Ando, Kurisu Tada, Kazuo Kempe, Hirofumi Amano, Ken Yamaji, Naoto Tamura, Yoshinari Takasaki  
Department of Rheumatology and Internal Medicine, Juntendo University

School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] Ascites in systemic lupus erythematosus (SLE) show variety of conditions such as good response to treatment, refractory cases, difficulty in diagnosis, secondary causes, and so on. Since systemic report about SLE with ascites is still rare, we report our analyzed cases. [Methods] We investigated 53 patients with ascites (4.7%) of 1139 SLE patients admitted to our hospital over the last 10 years, and checked their pathology, origin of ascites, and prognosis. [Results] The average age was 41.8 y.o., and male to female ratio was 1:12. Ascites caused by enteritis (22 cases, 41.5%), nephrose (16, 30.2%), peritonitis (5, 9.4%) and others (10, 18.9%). Eight cases with ascites died, and 3 cases out of 22 enteritis died (13.6%). [Conclusion] Most common etiology of ascites was due to hypoalbuminemia associated with lupus nephritis in SLE patient, but massive ascites was rare. Almost half of the cases were due to enteritis such as protein-losing enteropathy. One of the cases with massive ascites due to peritonitis found to have liver cirrhosis at autopsy, and indicated that we must take care of not only single origin, but also complex factors. Although lupus enteritis generally shows good response to medication, careful attention should be paid for refractory and complicated cases.

### W81-1

#### The present state of pregnancy and delivery of patients with rheumatoid arthritis in our department

Akiko Sasaki<sup>1,2,3</sup>, Yuya Takakubo<sup>1,2</sup>, Suran Yang<sup>1,3</sup>, Yasushi Naganuma<sup>1,3</sup>, Hiroharu Oki<sup>1</sup>, Hiroshi Oorui<sup>4</sup>, Michiaki Takagi<sup>1,2,3</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Yamagata University School of Medicine, Yamagata, Japan, <sup>2</sup>Yamagata Saisei Hospital, Yamagata, Japan, <sup>3</sup>Yoshioka Hospital, Yamagata, Japan, <sup>4</sup>Yamagata Hospital, Yamagata, Japan

Conflict of interest: None

[Objectives] We investigated the present state of pregnancy and delivery of patients with rheumatoid arthritis (RA). [Method] RA patients visiting a hospital for treatment in our department, the case that became pregnant or deliver from 2009 to 2014. We investigated age at pregnancy, a contraction of disease, disease activity score (DAS) 28 CRP, medication and the perinatal situation. [Results] There were 17 pregnancy and 13 delivery, the whole pregnancy were four cases. The average age at pregnant was 30.4 years old, and the contraction of disease was 8.7 years. DAS28CRP before pregnancy was 2.42, but it was increased during pregnancy. Furthermore, it was increased more after delivery. At the pregnant, 11 cases were administered biologics, three cases were given conventional DMARDs except MTX. All cases discontinued biologics and DMARDs, were given PSL or NSAIDs during pregnancy. However, one case was increased disease activity awfully all over the course, resumed biologics administration. At the delivery, two cases were low weight children, one case was premature birth, apnea and cesarean section, respectively. However there was not case for the growth. [Conclusion] Eleven women became pregnant during RA treatment, and six women of those experienced second pregnancy.

### W81-2

#### What kind of influence RA has had on the woman

Sari Takahashi, Yoshiko Sasaki, Masataka Komagamine  
Komagamine Rheumatoid Orthopaedic Clinic

Conflict of interest: None

[Objectives] We carried out a survey HAQ of female outpatients of RA and other diseases, and conducted an investigation and analysis about the kind of influence RA has on women. [Methods] Patients ages 20 to 70 filled out survey about education, work, marriage, childbirth and HAQ. Results were divided/compared in three groups; 1st group RA: HAQ in remission, 70 cases, age 62.4. 2nd group RA: HAQ poor condition, 13 cases, age 57.1. 3rd group other diseases: 82 cases, age 71.9. (3 HAQ poor cases of other diseases were excluded) [Results] This is significant difference. 1.72 is small number compared with average of 2.20 for the respondents born after 1943. HAQ were 0.08/0.97/0.07 for each

group. Although there is a difference of age (16.4) between 2nd and 3rd group, 2nd group showed high HAQ score in younger average age group. [Conclusion] RA patient's unemployment rate was higher than general unemployment rate (3.71%), and average number of children was lower in the RA patients HAQ poor condition group. HAQ poor condition patients have more difficulty in ADL than elderly people of other diseases, so RA had a big influence in female life.

### W81-3

#### The evaluation of work disability in patients with rheumatoid arthritis -the TOMORROW study-

Shohei Anno<sup>1,4</sup>, Yuko Sugioka<sup>2,3</sup>, Kenji Mamoto<sup>2</sup>, Tadashi Okano<sup>2</sup>, Masahiro Tada<sup>2</sup>, Kentaro Inui<sup>2</sup>, Tatsuya Koike<sup>1,3,4</sup>

<sup>1</sup>Shirahama Hamayu Hospital, Wakayama, Japan, <sup>2</sup>Dept. of Orthopedic Surgery, Osaka City University Medical School, Osaka, Japan, <sup>3</sup>Center for Senile Degenerative Disorder, Osaka City University Medical School, Osaka, Japan, <sup>4</sup>Serch Institute for Bone and Arthritis Disease, Wakayama, Japan

Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) may impair work productivity and daily activity, because of the joint disorders. We assessed the work disability in patients with RA participated in the TOMORROW study. [Method] The participants in the study were consisted 192 RA patients and 192 age- and sex-matched healthy volunteers (Vo). Work-related outcomes were measured using the WPAI by each employment status (Paid Worker [PW] employed for  $\geq 35$  hours/week, Part Time Worker [PTW], or Home Worker [HM]). The health status and the daily activities were assessed by EQ-5D and HAQ. [Result] There was no significant difference in percentages of the employment status (RA; PW/PTW/HW=18/17/65, Vo; 18/25/58), the absenteeism (RA; PW/PTW=0/6.3, Vo; 0/16.7), the presenteeism (RA; PW/PTW=18/14.4, Vo; 11.7/13.2) and overall work impairment (OWI) between two groups. Percentage of activity impairment (AI) of HW was higher in RA patients than that of in Vo (RA/Vo: 39/12,  $p < 0.001$ ). In RA patients, HW had lower EQ-5D and higher HAQ and DAS28 scores than paid workers. [Conclusion] Surprisingly there was no significant difference in employment status and work impairment between two groups among paid workers. HW with RA had daily activity impairment and high disease activity compared to working RA patients.

### W81-4

#### The effects of MTX or biological therapeutics on work productivity and activity impairment (WPAI) for patients with rheumatoid arthritis

Saori Takemoto<sup>1</sup>, Miyuki Itou<sup>1</sup>, Tomoko Nosyo<sup>1</sup>, Yuriko Iwasaki<sup>1</sup>, Yasushi Tanaka<sup>2</sup>, Ryosuke Yoshihara<sup>2</sup>, Miki Murata<sup>2</sup>, Kazuko Shiozawa<sup>2</sup>

<sup>1</sup>Nursingpart, Kohnan Kakogawa Hospital, <sup>2</sup>Kohnan Kakogawa Hospital, Rheumatic Center

Conflict of interest: None

(Purpose) Patients with RA were treated with MTX alone (n=48) or BIO (Bio n=47) Disease activities and WPAI were assessed by CDAI and WPAI-RA questionnaire for 48 weeks. (Result) Patients receiving BIO demonstrated significant and rapid improvement in disease activity compared with those receiving MTX. Mean CDAI at baseline, week 12, 24, and 48 were 24.96, 9.25, 5.38, and 4.14 in the Bio group, and 19.72, 13.39, 11.02, and 9.75 in the MTX group, respectively. The Bio group was statistically superior to the MTX group for CDAI at week 24 and 48 ( $p < 0.05$ ). Among CDAI variables, patient's global assessment of disease activity on Pt-VAS was most significantly improved. Pt-VAS at baseline, week 12, 24 and 48 were 48.64, 21.23, 13.89, and 9.88 in the Bio group, and 39.96, 31.26, 25.14, and 20.32 in the MTX group, respectively. Changes in WPAI scores in the Bio group from baseline to week 24 and 48 were 16.84% and 8.13%, while those in the MTX group were 30.3% and 8.13%. (Conclusion) Compared with MTX, biological therapeutics for patients with RA could provide more significant and rapid improvement in disease activities and work productivity. Patient Pt-VAS was markedly improved among CDAI variables, suggesting that patient's subjective symptoms might influence on their work productivity.

## W81-5

### Cost-effectiveness analysis of DMARDs and biologics therapy (annual report from NinJa 2013) -The increase of DMARDs' cost is continuing -

Yasuo Suenaga<sup>1</sup>, Toru Masuda<sup>1</sup>, Shigeto Tohma<sup>2</sup>, Jinju Nishino<sup>3</sup>

<sup>1</sup>Department of Rheumatology, Beppu Medical Center, NHO, Oita, Japan, <sup>2</sup>Department of Rheumatology, Sagami National Hospital, NHO, Kanagawa, Japan, <sup>3</sup>Nishino Clinic, Orthopaedics and Rheumatology

Conflict of interest: None

[Objectives] To evaluate the balance between the clinical effects of recent anti-rheumatic treatment and its cost by following up the annual change of them. [Method] The Data from RA patients registered in the large cohort database (NinJa) in 2002-2013 was analyzed. They included disease activity, mHAQ, and dosage of DMARDs. The annual cost-effectiveness calculated from clinical index and the cost of DMARDs. [Results] The averages of DAS28, SDAI, and mHAQ were decreasing and the percentages of patients with low disease activity or remission were increasing constantly. The annual cost of DMARDs was about 480,000 yen / patient in 2013. That was 50,000 yen higher than the cost in 2012. The rate of the cost of biologics for total DMARDs' cost was 73.3%. That decreased slightly. ([The rate of the number of low activity patients to that of high activity patients] / cost) increased since 2009 and reached near the level in 2003 (pre-bio-era in Japan), but the rate of increase decreased in 2013. [Conclusion] The increase of the DMARDs' cost almost stopped in 2012, but restarted in 2013. The cost-effectiveness of DMARDs was improving, but the rate of improvement decreased in 2013. If the increase of the cost does not stop, the cost-effectiveness may become worse next year.

## W81-6

### Smart device may provide the accuracy increase and streamlined process in the medical care of patients with rheumatoid arthritis

Keigo Ikeda<sup>1</sup>, Hisaaki Uehara<sup>1</sup>, Kozo Watanabe<sup>1</sup>, Takuya Hirai<sup>1</sup>, Kana Tanji<sup>1</sup>, Yoshinari Takasaki<sup>2</sup>, Iwao Sekigawa<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Juntendo University Urayasu Hospital, Chiba, Japan, <sup>2</sup>Department of Internal Medicine and Rheumatology, Juntendo University, School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] Various biologic agents and new scales of disease activity have developed the medical care of rheumatoid arthritis (RA). However, medical experts have been required to manage a wide variety of medical information related to RA patients such as medication history. We therefore developed the system using smart device and evaluated the benefit for medical experts to grasp the condition and treatment status of patients before the examination. [Methods] 40 RA patients inputted information relevant to the condition and health assessment questionnaire to a smart device before the examination. The efficacy was assessed by shortening input time at every visit and results of questionnaire from both patients and medical experts. [Results] Input time was shortening in most of patients at every visit. There were no problems for patients with weak eyesight or severe arthropathy, through a study time. Additionally, both patients and medical experts admitted the system as effective in a questionnaire. [Conclusion] The medical support system using smart device showed the possibility to provide the accuracy increase and streamlined process in the medical care of RA patients.

## W82-1

### What is the difference in treatment of RA between physicians and orthopaedic surgeons?-Analysis of NinJa 2013 -

Koichiro Takahi<sup>1</sup>, Jinju Nishino<sup>2</sup>, Hiroyuki Nakaya<sup>1</sup>, Kazuhiko Imoto<sup>1</sup>, Shigeto Tohma<sup>3</sup>

<sup>1</sup>Dept. of Orthopaedic Surgery, Toneyama National Hospital, Toyonaka, Japan, <sup>2</sup>Dept. of Orthopaedic Surgery, The University of Tokyo Hospital, <sup>3</sup>Division of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital

Conflict of interest: None

[Objective & Methods] To bring out the difference of treatment between doctors, 12,962 patients with RA collected for NinJa 2013 data base were divided to three groups according to their doctor (s): physician (81.3%), orthopaedic surgeon (15.6%) and both (3.1%). [Results] Average age and disease duration: 66.3, 66.1 and 66.9 y.o. and 11.2, 16.3 and 21.5 ys. Rates of treated with PSL or MTX and average doses of MTX: 45.4, 34.5 and 67.0%, 65.3, 59.5 and 62.8% and 8.4, 7.7 and 7.8mg/wk. Rates of treated with biologics: 23.6, 34.5 and 30.4%, while patients number who operated with total arthroplasty: 8.3, 29.3 and 56.2 /1000 patients. Average CRP: 0.59, 0.70 and 0.74mg/dl, DAS28-CRP: 2.43, 2.7 and 2.51, and rates of remission (DAS28 CRP<2.3): 52, 41 and 49%. Average mHAQ: 0.373, 0.589 and 0.958 and rates of remission (mHAQ ≤0.5): 76.4, 61.9 and 40%. [Discussion & Conclusion] Physicians treated patients with more PSL and MTX, while patients with orthopaedic surgeons were with longer disease duration, more complicated with physical ability and experienced more operations and biologic treatment. Hence the latter might be more progressed and severe states of RA. We concluded that the character of patients is different between physician and orthopaedic surgeon.

## W82-2

### An attitude survey on RA treatment of clinicians in northeastern Osaka

Yoshio Ozaki<sup>1,2</sup>, Tohru Nishizawa<sup>2</sup>, Hideki Amuro<sup>2</sup>, Yonsu Son<sup>1,2</sup>, Hideo Kagawa<sup>3</sup>, Tsuyoshi Teranishi<sup>4</sup>, Shigeo Miyashima<sup>5</sup>, Tomoki Ito<sup>2</sup>, Shosaku Nomura<sup>2</sup>

<sup>1</sup>Department of Rheumatology and Clinical Immunology, Kansai Medical University Hirakata Hospital, Hirakata City, Japan, <sup>2</sup>First Department of Internal Medicine, Kansai Medical University, Hirakata City, Japan, <sup>3</sup>Medical Corporation - Kagawa-Clinic, Neyagawa City, Japan, <sup>4</sup>Teranishi Naika, Kadoma City, Japan, <sup>5</sup>Miyashima RA & Orthopaedic Clinic, Hirakata City, Japan

Conflict of interest: None

[Objectives] Kitakawachi region in northeastern Osaka has a population of 1.2 million people. The region has few flagship hospitals, and the majority of examinations and medical treatments for rheumatoid arthritis (RA) are performed in clinics. We conducted a sentiment survey to build a collaborative system for continuous and effective RA medical examination. [Methods] The survey was distributed to 940 facilities, including internal medicine and orthopedic surgery departments of hospitals and clinics. [Results] Responses were obtained from 284 facilities (30.2%). The majority of responses (164) were from facilities with less than 10 RA patients, and 5 facilities have more than 100 patients. Some facilities (38) have a policy to "provide treatment to patients with no high-risk symptoms." Other facilities (69) "avoid direct treatment if possible." The main reason for avoidance was "we do not know the standard selection of medication" (53). [Conclusion] Some clinics use high-dose methotrexate (MTX) and biological agents for RA. Other clinics reported that MTX is not their first choice for RA treatment. We concluded that clarification of local policies and strengthening of collaboration are necessary to standardize medical treatment for RA.

## W82-3

### Anxiety and Depression Factors in Patients with Rheumatoid Arthritis -Study using KURAMA cohort-

Miyabi Uda<sup>1</sup>, Kazuko Nin<sup>1</sup>, Motomu Hashimoto<sup>2</sup>, Mie Torii<sup>3</sup>, Takao Fujii<sup>2</sup>, Akiko Hanai<sup>1</sup>, Masahiro Ishikawa<sup>2</sup>, Moritoshi Furu<sup>2</sup>, Hiromu Ito<sup>2,4</sup>, Masahide Hamaguchi<sup>5</sup>, Chikashi Terao<sup>6</sup>, Wataru Yamamoto<sup>2,7</sup>, Tsuneyo Mimori<sup>8</sup>

<sup>1</sup>Department of Human Health Science, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>2</sup>Center for Rheumatic Diseases, Kyoto University Hospital, Kyoto, Japan, <sup>3</sup>Research and Education Unit of Leaders for Integrated Medical System, Kyoto University, Kyoto, Japan, <sup>4</sup>Department of Orthopaedic Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>5</sup>Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>6</sup>Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan, <sup>7</sup>Department of Health Information Management, Kurashiki Sweet Hospital, Okayama, Japan, <sup>8</sup>Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University,



Kyoto, Japan

Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) patients have been reported to easily merge anxiety and depression symptoms due to pain, functional disability, and reduced social interaction. In this study, we examined the factors that influence their anxiety and depression levels. [Methods] We investigated the correlation between anxiety and depressive symptoms and increased disease activity, physical dysfunction, medication status in RA patients (n=410), as measured by HADS (Hospital Anxiety and Depression Scale). [Results] Of all patients, 20.4% were found to have anxiety; 30.2% to have depressive symptoms. In logistic regression analysis, simplified disease activity index (SDAI) effects anxiety (OR1.07,  $p = 0.007$ ); use of steroids effects depressive symptoms (OR1.81,  $p = 0.028$ ). Through linear regression methods with multivariate analysis, SDAI remission patients showed lower anxiety compared to non-remission patients ( $4.10 \pm 0.34$  vs  $5.37 \pm 0.27$ ,  $p = 0.004$ ). Patients using steroids had higher depression total scores compared to steroid-free patients ( $6.67 \pm 3.75$  vs  $5.50 \pm 3.68$ ,  $p = 0.058$ ). [Conclusion] The results suggest the levels at which anxiety symptoms are reduced in RA disease remission in the cohort, and suggest that depressive symptoms increase when steroids are prescribed as part of RA treatment.

## W82-4

### Survey of anxiety in rheumatoid arthritis patients to whom the self-injection of biologic agents are introduced: Follow-up study for three years

Miwa Ueda<sup>1</sup>, Katsumi Ito<sup>1</sup>, Takuo Juji<sup>1</sup>, Ichiro Nakamura<sup>1,2</sup>

<sup>1</sup>Department of Rheumatology, JCHO Yugawara Hospital, <sup>2</sup>Faculty of Medical Science for Health, Teikyo Heisei University

Conflict of interest: None

[Objectives] Etanercept, adalimumab, tocilizumab and abatacept could be prescribed for rheumatoid arthritis (RA) patients by self-injection. The purpose of this study is to investigate qualitatively and quantitatively the anxiety of RA patients to whom self-injection of biologic agents is introduced. [Methods] The objects are 42 patients with RA (mean age, 55.5 years old; mean duration of RA, 15.9 years) to whom etanercept or adalimumab were first time introduced and maintained for 3 years. [Results] The quantity of anxiety of RA patients before the self-injection introduction was an average of 52.6/100 mm in visual analog scale (VAS), which significantly decreased with an average of 17.6/100 mm at 6 months. Even 3 years after the self-injection introduction, VAS of anxiety is still maintained to a low value (26.0/100 mm). The contents of anxiety were curative effects (38.1%), side effects (59.5%), procedure of injection (52.4%), fear over a needle (33.3%), and economical burden (38.1%). Although anxiety decreased in all items after self-injection introduction, uneasiness to an economical load and unexpected side effects still remained at moderate value for 3 years. [Conclusion] A continuous psychological support is necessary for RA patients to whom biologic agents are introduced.

## W82-5

### Attitude survey on the role of the nurse involved in medical care for patients with rheumatoid arthritis~Utilizing EULAR recommendations for the role of the nurse ~

Mie Fusama<sup>1</sup>, Hideko Nakahara<sup>2,3</sup>, Tsutomu Takeuchi<sup>4</sup>

<sup>1</sup>Division of Nursing, NTT West Osaka Hospital, <sup>2</sup>Division of Allergy, Rheumatology and Connective Tissue Diseases, Department of Internal Medicine, NTT West Osaka Hospital, <sup>3</sup>Kansai Health Administration Center, NTT West Corporation, <sup>4</sup>Division of Rheumatology Department of Internal Medicine School of Medicine, Keio University

Conflict of interest: None

Objectives: The aim of this study is to ask nurses (Ns) and doctors (Dr) in Japan on agreement and application to EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis. Methods: Subjects: Ns and Dr involved in medical care for RA. Periods: Oct.-Nov, 2014. On 10 recommendations, we evaluated levels of

agreement and application using a 0-10 rating scale. Results: Ns 322 (M/F: 7/315), Dr 69 (M/F: 59/10). Average age of Ns/Dr: 42/43 years. Clinical Experiences for RA: 5.2/12.6 years. On all items, levels of application were significantly lower than those of agreement in both Ns and Dr. Comparing Ns with Dr on agreement, no significant difference was found in all 10 items. Levels of application were significantly lower in Ns on 9 items. Suggesting continuous education to improve and maintain knowledge and skills was agreed with Ns and Dr. Insufficient knowledge and lack of time in Ns were considered for reasons of discrepancies. Conclusion: As for recommendations for the roles of Ns in EULAR, levels of application were significantly lower compared with agreement in both Ns and Dr in Japan and there were discrepancies between Ns and Dr in application. These results indicate problems in future to be solved, establishing roles of Ns.

## W82-6

### Survey on Recognition of EULAR Recommendations by Nurses engaged in RA Care

Mayumi Kaneko, Shigeru Honjo

Honjo Rheumatism Clinic

Conflict of interest: None

[Objectives] A presentation about the role of nurses was given at ACR2013. It was suggested that EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis have been fully understood but it is impossible to implement the recommendations under the present circumstances. This time, we understood the present situation of RA care and highlighted future challenges by a survey on recognition and practice degree of these recommendations. [Methods] The survey for nurses involved in RA care was carried out using mail questionnaires and questionnaires answered at the meeting venue. [Results] 186 out of 202 results were adequate to be assessed. The recognition degree of all the recommendations was low as 16.6%, and the group with recognition of the recommendations tends to implement the recommendations more than the other group without it. [Conclusion] The survey results showed that the recognition of the recommendations is low and there are gaps between ideal and reality. Educating nurses for dissemination of the EULAR recommendations at a workshop for nurses is considered necessary. In addition, the practice of RA nursing is expected to be improved by sharing information of RA care through nurses' network.

## W83-1

### Treatment response of biological agents in elderly rheumatoid arthritis

Shoko Tateishi<sup>1,2</sup>, Hiroko Kanda<sup>1,2</sup>, Harumi Shirai<sup>2</sup>, Yasuo Nagabuchi<sup>2</sup>, Kazuyoshi Ishigaki<sup>2</sup>, Yu Seri<sup>2</sup>, Toshiki Eri<sup>2</sup>, Lisa Akahira<sup>2</sup>, Miho Oshima<sup>2</sup>, Yumi Yamaguchi<sup>2</sup>, Yuta Kochi<sup>2</sup>, Eri Kinoshita<sup>2</sup>, Satoshi Shinohara<sup>2,3</sup>, Oh Sasaki<sup>2</sup>, Yukiko Iwasaki<sup>2</sup>, Hiroaki Harada<sup>2</sup>, Mihoko Shibuya<sup>2</sup>, Shuji Sumitomo<sup>2</sup>, Hirofumi Shoda<sup>2</sup>, Kanae Kubo<sup>2</sup>, Fujio Takeuchi<sup>2</sup>, Keishi Fujio<sup>2</sup>, Kazuhiko Yamamoto<sup>2</sup>

<sup>1</sup>Department of Immunotherapy Management, Graduate School of Medicine, University of Tokyo, Tokyo, Japan, <sup>2</sup>Department of Allergy and Rheumatology, The University of Tokyo, Tokyo, Japan, <sup>3</sup>Tochigi Rheumatic Clinic, Utsunomiya, Japan

Conflict of interest: Yes

[Objectives] In an aging society in Japan, biologics have been widely used for elderly people for the treatment of RA. The objective was to determine the comparative efficacy of biologics in elderly RA in our hospital. [Methods] Patients were 26 elderly RA ( $y \geq 65$ ) and 41 young RA ( $65 > y$ ) who were started biologics in our hospital. Outcomes were the mean differences in DAS 28-CRP, DAS 28-ESR, SDAI, CDAI for biologics compared elderly RA with young RA at baseline, 3,6,9 and 12-months (mo.). And also we compared to DASCRP in the difference of using with or without Methotrexate (MTX). [Results] At 3-mo., young RA was in remission or had low disease activity (LDA) in the mean of DASCRP, DASESR, SDAI and CDAI. Elderly RA had LDA in DASCRP at 9-mo., in SDAI and CDAI at 6-mo. and did not have LDA in DASESR by 12-mo. By the difference of the dosage of MTX, all of young RA had

LDA in DASCRP at 3-mo. Elderly RA with high dose MTX ( $\geq 8\text{mg/w}$ ) had LDA in DASCRP at 6-mo, with low dose MTX ( $2\text{-}6\text{mg/w}$ ) at 9-mo. [Conclusion] For elderly RA, it need time to take effect of the biologics compared to young RA. But elderly RA with high dose MTX was able to reach LDA more quickly than with low dose MTX and without MTX, and had also lower disease activity at 12-mo.

### W83-2

#### Fracture surgeries in rheumatoid arthritis patients: from the "Ninja" registry

Norie Yoshikawa<sup>1</sup>, Koichiro Saisho<sup>1</sup>, Shigeto Tohma<sup>2,3</sup>, Ko Sugata<sup>1</sup>, Etsuo Chosa<sup>4</sup>, Hiroaki Hamada<sup>4</sup>, Jinju Nishino<sup>5</sup>

<sup>1</sup>Department of Orthopedics and Rheumatology, National Hospital Organization Miyakonojo Hospital, Miyakonojo, Japan, <sup>2</sup>iR-net, <sup>3</sup>Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami National Hospital, Sagami, Japan, <sup>4</sup>Department of Orthopedics, Miyazaki University, Miyazaki, <sup>5</sup>Nishino Orthopedics and Rheumatology Clinic

Conflict of interest: None

[Objectives] The aim of this study was to investigate for drug use of rheumatoid arthritis (RA) patients who injured the fracture of limbs requiring surgery using National Database of Rheumatic Diseases by iR-net in Japan (Ninja). [Methods] Presence or absence, injury site, drug use, etc. of fracture surgeries examines in 13285 patients registered in 2013 (1,0654 females, 2631 males). [Results] There were 62 females patients 10 males patients (Stage I: 9, II: 6, III: 14, IV: 35. Class 1: 9, 2: 30, 3: 21, 4: 5), with a mean age of 71.8 years. 10 RA patients were drug free. Of the remaining 62 RA patients, there were 30 (41.7%) patients treated methotrexate (MTX), 14 (19.4%) patients treated biologic agent (Bio), 15 (20.8%) patients treated DMARDs. The mean oral steroid dose was 2.9 mg/day prednisolone. [Conclusion] There was a trend for a MTX group and a Bio group have low fracture rate.

### W83-3

#### A risk factor for fracture in patients with rheumatoid arthritis is not the disease itself but the use of glucocorticoid –the 4th year results of the TOMORROW study-

Yuko Sugioka<sup>1</sup>, Tatsuya Koike<sup>1,2</sup>, Kenji Mamoto<sup>3</sup>, Tadashi Okano<sup>3</sup>, Masahiro Tada<sup>3</sup>, Kentaro Inui<sup>4</sup>, Hiroaki Nakamura<sup>3</sup>

<sup>1</sup>Center for Senile Degenerative Disorders (CSDD), Osaka City University Medical School, Osaka, Japan, <sup>2</sup>Search Institute for Bone and Arthritis Disease (SINBAD), Shirahama Foundation for Health and Welfare, Wakayama, Japan, <sup>3</sup>Orthopaedic Surgery, Osaka City University Medical School, Osaka, Japan, <sup>4</sup>Rheumatology, Osaka City University Medical School, Osaka, Japan

Conflict of interest: None

**Background:** Patients with rheumatoid arthritis (RA) who have muscle weakness might be at increased risk of fracture. The present study prospectively determines the incidence of fractures and their risk factors in patients with RA who participated in the TOMORROW study that began in 2010. **Methods:** We evaluated anthropometric parameters, BMD, disease activity and the occurrence of fractures for a period of 4 years in 208 RA (58 y) and 205 age- and gender-matched volunteers (Vo: 57 y). **Results:** There is no difference in incidence of fractures between RA (14.9%) and Vo (9.4%) during 4 years. After adjusting for risk factors for fractures, multiple regression analysis revealed that prevalence of vertebral fracture (odds ratio [OR], 2.80;  $p = 0.002$ ) and glucocorticoid (GC) medication at entry (OR, 2.90,  $p = 0.002$ ) was the associated with the incidence of fractures in whole population. However, there is no association with morbidity of RA and incidence of fractures. In RA, GC medication at entry was a significant parameter associated with incidence of fractures. (OR: 3.01,  $p=0.001$ ) **Conclusions:** The incidence of fractures did not significantly differ between patients with RA and Vo during a period of 4 years. Medicating with GC was apparently associated with the incidence of fractures

### W83-4

#### Analysis of surgeries related to rheumatoid arthritis using NinJa during fiscal year 2013

Koichiro Saisho<sup>1,2</sup>, Shigeto Tohma<sup>2,3</sup>, Norie Yoshikawa<sup>1</sup>, Ko Sugata<sup>1</sup>, Etsuo Chosa<sup>4</sup>, Hiroaki Hamada<sup>4</sup>, Jinju Nishino<sup>5</sup>

<sup>1</sup>Department of Orthopedics and Rheumatology, National Hospital Organization Miyakonojo Hospital, Miyakonojo, Japan, <sup>2</sup>iR-net, <sup>3</sup>Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami National Hospital, Sagami, Japan, <sup>4</sup>Department of Orthopedics, Miyazaki University, Miyazaki, <sup>5</sup>Nishino Orthopedics and Rheumatology Clinic

Conflict of interest: None

[Objectives] Analyze/report RA-related orthopedic surgeries performed in '13 using NinJa. [Methods] Presence or absence, type, frequency, etc. of surgeries examined in 13285 patients registered in '13 (1,0654 women, 2631 men) & compared with '03 to '13. [Results & conclusion] Of 13285 patients in '13, 353 patients/415 events (2.7%/3.1%) underwent RA surgeries. The number of RA surgery cases decreased from 8.5% in '03 to 3.1% in '13. In '13, RA surgeries to total patient number ratios were (per type) 1.6% (TJA), 3% (synovectomy), 0.73% (arthroplasty), 0.24% (arthrodesis), 0.08% (tendon repair) & 0.11% (revision TJA). Medication: 64.5%, 25.4% and 0.23% of patients received total MTXs, total biologics & total JAK inhibitors, respectively: an increase. In the main-Bio group, the rate of RA surgery peaked at 15% in '06 and decreased thereafter to 4.4% in '13. In the main-MTX group, the rate of surgery also decreased from 9.5% in '03 to 3.1% in '13. Among patients receiving JAK inhibitors, three surgeries had been performed. Although the number of surgeries decreased with increasing use of drugs in the Bio and MTX groups, the rate of decrease was decreasing. We plan to continue to follow up on changes in surgery rates with the emergence of new drugs such as JAK. Follow up planned.

### W83-5

#### Five-year longitudinal study of AORA (Akita Orthopedic group on Rheumatoid Arthritis) registry data

Seiya Miyamoto<sup>1</sup>, Yoichi Kataoka<sup>2</sup>, Masaaki Ogino<sup>3</sup>, Hiromi Morita<sup>4</sup>, Kunitaka Yang<sup>5</sup>, Wataru Watanabe<sup>6</sup>, Nobuhiro Ishizawa<sup>7</sup>, Kazuhiro Shoji<sup>8</sup>, Natsuo Konishi<sup>9</sup>, Hidetoshi Watanabe<sup>10</sup>, Takeshi Kashiwagura<sup>11</sup>, Masakazu Urayama<sup>12</sup>, Hiroki Ito<sup>13</sup>, Moto Kobayashi<sup>14</sup>, Tsutomu Sakuraba<sup>14</sup>, Toshiaki Aizawa<sup>15</sup>, Keiji Kamo<sup>16</sup>, Hiroshi Aonuma<sup>17</sup>, Yusuke Sugimura<sup>18</sup>, Naohisa Miyakoshi<sup>19</sup>, Yoichi Shimada<sup>19</sup>

<sup>1</sup>Department of Orthopedic Surgery, Nakadori General Hospital, Akita, Japan, <sup>2</sup>Joto Orthopedic Clinic, Akita, Japan, <sup>3</sup>Department of Orthopedic Surgery, Koto Kousei Hospital, Akita, Japan, <sup>4</sup>Morita Orthopedic Clinic, Akita, Japan, <sup>5</sup>Yang Orthopedic Clinic, Akita, Japan, <sup>6</sup>Department of Orthopedic Surgery, Honjo Daiichi Hospital, Akita, Japan, <sup>7</sup>Department of Orthopedic Surgery, Fujiwara Memorial Hospital, Akita, Japan, <sup>8</sup>Shoji Orthopedic Clinic, Akita, Japan, <sup>9</sup>Department of Orthopedic Surgery, Akita Kousei Medical Center, Akita, Japan, <sup>10</sup>Watanabe Orthopedic Clinic, Akita, Japan, <sup>11</sup>Department of Rehabilitation Medicine, Akita City Hospital, Akita, Japan, <sup>12</sup>Department of Orthopedic Surgery, Ogachi Central Hospital, Akita, Japan, <sup>13</sup>Department of Orthopedic Surgery, Yamamoto Kumiai General Hospital, Akita, Japan, <sup>14</sup>Department of Orthopedic Surgery, Hiraka General Hospital, Akita, Japan, <sup>15</sup>Department of Orthopedic Surgery, Kita Akita Municipal Hospital, Akita, Japan, <sup>16</sup>Department of Orthopedic Surgery, Akita Rosai Hospital, Akita, Japan, <sup>17</sup>Department of Orthopedic Surgery, Kakunodate Municipal Hospital, Akita, Japan, <sup>18</sup>South Akita Orthopedic Clinic, Akita, Japan, <sup>19</sup>Department of Orthopedic Surgery, Akita University Graduate School of Medicine, Akita, Japan

Conflict of interest: None

[Background] We report our 5-year longitudinal AORA registry study data. [Subjects and Methods] Patients received treatment from 36 doctors at 28 AORA institutions from 2010 to 2014. We conducted annual data compilations and examined age, sex, comorbidities, oral medications, disease activity, and biological agent use. [Results] Patient numbers were 1194, 1533, 1665, 1843, and 1987 in 2010, 2011, 2012, 2013, and 2014, respectively, a 10% increase per year. About 80% were women, and the most common comorbidity was hypertension (30%). Methotrexate was given to 50% of patients, with the dosage increased from 5.98

(2010) to 7.01 mg/week (2014); prednisolone was given to 50%, with the dosage being about 4 mg during the study. Disease-modifying anti-rheumatic drugs were given to 85% of patients, with 70% receiving bucillamine and/or salazosulfapyridine. The DAS28-ESR score was 3.18 in 2012, 3.10 in 2013, and 3.04 in 2014, and 60% of patients had low disease activity. Biological agents were used for treating 593 patients in total with the mean age of 58 years.

### W83-6

#### Background characteristics of the RA patients with multiple joint disorders who are going to take joint reconstructive surgery

Masayo Kojima<sup>1</sup>, Toshihisa Kojima<sup>6</sup>, Hajime Ishikawa<sup>3</sup>, Keiichiro Nishida<sup>8</sup>, Jun Hashimoto<sup>10</sup>, Hisaaki Miyahara<sup>13</sup>, Sakae Tanaka<sup>7</sup>, Nobuhiko Haga<sup>9</sup>, Yasuo Niki<sup>11</sup>, Naoki Ishiguro<sup>2</sup>

<sup>1</sup>Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, <sup>2</sup>Department of Orthopaedic Surgery Faculty of Medicine, Nagoya University, <sup>3</sup>Department of Orthopaedic Surgery, Niigata Rheumatic Center, <sup>4</sup>Department of Orthopaedic Surgery, Nagoya University Hospital, <sup>5</sup>Department of Orthopaedic Surgery, The University of Tokyo, <sup>6</sup>Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, <sup>7</sup>Department of Rehabilitation, The University of Tokyo, <sup>8</sup>National Hospital Organization Osaka Minami Medical Center, <sup>9</sup>Department of Orthopaedic Surgery School of Medicine, Keio University, <sup>10</sup>National Hospital Organization Kyushu Medical Center

Conflict of interest: None

[Objectives] The purpose of this study was to explore when and under what circumstances what type of surgical intervention could be offered to RA patients. [Methods] In the institutes participating in the study, RA patients who were going to take joint reconstructive surgery and provided consents to join the study were registered consecutively. After anonymous at each institution, the data were integrated and aggregated analyses were conducted for each major surgical site. A significance level of  $p < 0.05$  was adopted. [Results] During September, 2012 to November, 2013, a total of 360 patients have been registered. Women accounted for 74.5% of 349 patients. The average age was 65.1 (standard deviation 11.3) years of age and mean disease duration was 19.0 (10.6) years. No significant gender difference was observed except in CRP and MMP3. Variables which showed significant differences by surgery sites were disease duration, BMI, depression score (BDI-II), DAS28-CRP, Pain VAS, MMP3, and Steinblocker stage. [Conclusion] It became clear that a certain tendency could be observed in the patient characteristics by surgical sites. We are going to investigate the post-operative follow-up data to find the clues to propose the optimal treatments.

## The Subcommittee on Gender Equality Support Program

### GES-1

#### From the start at dendritic cell research towards the promotion of gender equality through supporting women researchers

Kayo Inaba

Executive Vice-President for Gender Equality, International Affairs, Public Relations, Director of Gender Equality Center, Graduate School of Biostudies, Kyoto University

Conflict of interest: None

I have been working on the dendritic cell research over 30 years by collaborating with Prof. Ralph M. Steinman, who was a Nobel Prize winner in Physiology and Medicine 2011, in the Rockefeller University. Results obtained from our work are now cited in the textbook of Biology for High School Student. This is extremely honorable for me. Dendritic cells have always fascinated me to continue experiments. However, once I got the position as an associate professor, I was assigned to other tasks and duties in the faculty as well as university, although my interest was still in research. The reason why I work now on present situation is sense of duty and responsibility. There were many triggers and corners that drew me from research to the current job, such as administration and management. In this session, I would like to briefly talk my research work and recollect what happened and pushed me to do in the past and present.

### GES-2

#### Woman Doctors Support Program in Division of Rheumatology, Showa University Hospital

Yusuke Miwa, Sakiko Isojima, Kumiko Otsuka, Mayu Saito, Masayu Umemura, Nao Oguro, Yoko Miura, Airi Nishimi, Ryo Takahashi, Tsuyoshi Kasama

Division of Rheumatology, Department of Medicine, Showa University School of Medicine

Conflict of interest: Yes

Woman doctors are limited their operation due to marry, pregnancy and delivery, and cannot show their ability to the maximum in a system built in viewpoint of male doctors. It has been quite a while since shortage of doctors was noticed, but it is true that there are potential woman doctors who do not make the most of their medical license sufficiently though they have it. In our Hospital, a system to adopt woman doctors who support their preschool children as special positions for part-time doctors in addition to quota of the university was admitted in pediatrics, obstetrics and gynecology, anesthesiology since 2009, and it was adapted in whole course in 2011. In medical profession, their duties are outpatient clinic, echo graphic examination, emergency duty in daytime, and doctor in charge in hospital ward. At least 3 doctors constitute a group in the ward and part-time doctors are in charge of inpatients as a member of the group. Although a doctor on duty should handle at night or on holiday in principle, part-time doctors do not urgently attend the hospital at night or on holiday. In education, their duties are lecture at medical and nursing school, training guidance for students in the hospital ward, guidance for residents. If they have skills or experiences as Rheumatologist, they are also in charge of instruction for young doctors who aim to be rheumatism specialists. As for their studies, they conduct clinical studies jointly with other staff at their pace and read their reports at our society. Significantly, it is necessary to observe the working hours, gain the understanding of other staff, establish a system to support them in case that their children suddenly become ill, their duties are unfinished, adjust their work volume according to their ability or capability. The system mentioned above would improve their skills related to medical treatment, education and study as Rheumatologist and enable them to obtain specialists, though times are restricted.

### GES-3

#### The Results of the Survey Conducted by the Subcommittee on Gender Equality Support

Yohko Murakawa<sup>1,2</sup>, Atsuko Murashima<sup>2,3</sup>, Kayoko Kaneko<sup>4</sup>, Ayako Nakajima<sup>2,5</sup>, Asami Abe<sup>2,6</sup>, Ayako Kubota<sup>2,11</sup>, Natsuko Nakagawa<sup>2,7</sup>,

Hitomi Haraoka<sup>2,8</sup>, Takako Miyamae<sup>2,5</sup>, Yu Funakubo<sup>2,9</sup>, Sachiko Miyake<sup>2,10</sup>

<sup>1</sup>Department of Rheumatology, Faculty of Medicine, Shimane University, Shimane, Japan, <sup>2</sup>the Subcommittee on Gender Equality Support Program, Japan College of Rheumatology, <sup>3</sup>Neonatal and Reproductive Medicine, National Center for Child Health and Development, Tokyo, Japan, <sup>4</sup>Division of Maternal Medicine, Center of Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, Tokyo, Japan, <sup>5</sup>Institute of Rheumatology, Tokyo Women's Medical University, <sup>6</sup>Dept. of Rheumatology, Niigata Rheumatic Center, <sup>7</sup>Kohnan Kakogawa Hospital, Rheumatic Center, <sup>8</sup>Division of Hematology and Rheumatology, Nihon University School of Medicine, <sup>9</sup>Houseikai Marunouchi Hospital, Nagano, Japan, <sup>10</sup>Juntendo University School of Medicine, <sup>11</sup>Department of Orthopaedic Surgery, Toho University School of Medicine, Tokyo, Japan

Conflict of interest: None

The 10-member Subcommittee on Gender Equality Support was established in April 2014. Women now account for more than 30% of the individuals who pass the state examination to receive a license to practice medicine. Additionally, women account for approximately 14% of the membership in the Japanese College of Rheumatology, and it has been estimated that this figure will gradually increase. Most universities and hospitals have recently been attempting to improve the conditions of women employees, such as by providing nursery schools, establishing committees focused on achieving a balance between work and life, and scheduling conferences during the day. How does the JCR promote and support its female members? The Government Gender Equality Bureau Cabinet Office proposed “the target of 30% by 2020”<sup>1</sup> with the aim of “increasing the share of women in leadership positions to at least 30% by 2020 in all fields in society”. This numerical target applies to women's participation and gender equality in a wide range of fields, including politics, national and local civil services, private sector enterprises, education, and research. Various efforts or “positive actions” are being undertaken by many companies and levels of government to expand women's participation. For example, the “Declaration on Action” was issued by a group of male leaders to create “A Society in which Women Shine.” In the future, women will account for 30% of those with a medical license. Our Subcommittee will facilitate the ability of female JCR members to assume important roles by developing their abilities and by offering opportunities for promotion. The JCR Secretariat emailed questionnaires to all JCR members to gather data about what we should do to create a society in which women's professional value is recognized and promoted. The questionnaire focused on members' (a) present professional status and satisfaction with work, (b) work–life balance, (c) career paths as doctors, and (d) attitudes toward gender equality. Based on the results, we discuss how our Subcommittee should proceed with regard to our women members. Increasing the proportion of female rheumatologists may also lead to an improved work–life balance among men. 1) [http://www.gender.go.jp/policy/positive\\_act/index.html](http://www.gender.go.jp/policy/positive_act/index.html)

## Anaphylaxis Guideline Program

### AP

#### Anaphylaxis guideline by Japanese Society of Allergology

Masao Yamaguchi

Division of Respiratory Medicine and Allergology, Department of Medicine, Teikyo University School of Medicine

Japanese Society of Allergology (JSA) set up a special committee for anaphylaxis on March in 2013 to prepare anaphylaxis guideline and establish a measure to anaphylaxis. Firstly, the committee had translated the World Allergy Organization (WAO) anaphylaxis guideline (developed in 2011) into Japanese and published the full text on Japanese Journal of Allergology (Arerugi) by the end of 2013. The committee then started to work on preparing JSA anaphylaxis guideline based on WAO guideline with reality in Japan. The committee decided a style of the guideline as simple as possible, open to public, and downloadable from JSA web. Anaphylaxis definitions in common use are: “a serious, life-threatening generalized or systemic hypersensitivity reaction” and “a serious allergic reaction that is rapid in onset and might cause death.” Definition and clinical diagnosis of anaphylaxis is based on the WAO guideline. Regarding epidemiology of anaphylaxis, we have little data in Japan so that we quoted data (Specified Report of Vital Statistics) of death by any kind anaphylactic shock from 2001 to 2013. Data vary year by year, but there seems an increasing trend of death of anaphylaxis by medications these days. Anaphylaxis typically occurs through an IgE-dependent mechanism, most commonly triggered by foods, stinging insect venoms, or medications. Medications can also trigger anaphylaxis through an IgE-independent mechanism and through direct mast cell activation. Radiocontrast media can trigger anaphylaxis through both IgE-dependent and IgE-independent mechanisms. Basic initial treatment of anaphylaxis is as follows. Remove exposure to the trigger, if possible and rapidly assess the patient's circulation, airway, breathing, mental status, and skin, and estimate the body weight. Promptly and simultaneously, call for help, inject adrenaline intramuscularly in the mid-anterolateral thigh, and place the patient on the back with the lower extremities elevated. When indicated at any point in time, as soon as the need is recognized, administer supplemental oxygen, insert an intravenous catheter and give intravenous fluid resuscitation, and initiate cardiopulmonary resuscitation with continuous chest compressions. At frequent and regular intervals, monitor the patient's blood pressure, cardiac rate and function, respiratory status and oxygenation and obtain electrocardiograms. The most important message by the JSA anaphylaxis guideline is that intramuscular injection of adrenaline should be an essential medication for the treatment of anaphylaxis. The guideline also emphasizes preparation of the patient for self-treatment of anaphylaxis recurrences in the community, confirmation of anaphylaxis triggers, and prevention of recurrences through trigger avoidance and immunomodulation.

## Poster Session

### P1-001

#### Exploration of the mechanisms of production with citrullinated proteins and its autoantibodies in autoimmune arthritis

Hoshimi Kawaguchi, Isao Matsumoto, Naoto Umeda, Asuka Inoue, Yuki Tanaka, Yuko Kurashima, Hiroshi Ebe, Takayuki Sumida  
Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

Conflict of interest: None

[Objectives] To explore the pathogenic relevance of citrullinated proteins (Cit-P) and its autoantibodies participate in peptide GPI-induced arthritis (pGIA). [Methods] 1) DBA/1 mice were immunized with pGPI325-339 to induce arthritis. 2) Cit-P expression in joints, skins and lungs were examined by immunohistochemistry. 3) The titres of anti-pGPI325-339 antibodies and ACPA in sera were analysed by ELISA. 4) C1-amidine (PAD inhibitor) were injected intraperitoneally to pGIA, and clinical score was assessed. [Results] 1) pGPI325-339 immunization induced symmetrical polyarthritis resembling rheumatoid arthritis in all mice. Arthritis appeared on day8, showed peak severity on day14 and then resolved slowly. 2) In immunohistochemistry, Cit-P was detected in joints on day14 and in skins on day7 with pGIA, whereas not detected with CFA immunized (control) mice. 3) The titres of anti-pGPI325-339 antibodies and ACPA in sera from pGIA were elevated after day14, and were significantly higher than those from control mice. 4) C1-amidine treatment significantly decreased clinical score. [Conclusion] Cit-P expression and the titer of ACPA were increased in pGIA, and the inhibition of PAD suppressed arthritis. These results suggest that PAD activity is involved with the pathogenesis and maintenance of arthritis.

### P1-002

#### Transgene dosage affects severity of rheumatoid arthritis and its complication, interstitial pneumonitis in RA model animal, D1CC mouse

Satoshi Kanazawa  
Department of Molecular and Cellular Biology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Conflict of interest: None

[Objectives] Collagen induced arthritis (CIA) which shows acute and transient disorder was used for study of rheumatoid arthritis (RA), however it was no report that CIA induced rheumatoid lung as a complication associated with RA. On the other hand, D1CC mouse shows RA with interstitial pneumonitis (IP). To reveal whether heterologous and homozygous transgenes affect these diseases development like human, I compared a clinical symptom of both of mice. [Methods] I established a novel rheumatoid arthritis mouse model called D1CC mouse, in which CIITA transgene was introduced as a master switch for MHC class II gene expression. Inflammatory arthritis was induced by injection of lower dose of type II collagen, because D1CC mice had high susceptibility to arthritogenic stimuli. It was concluded that D1CC mouse developed inflammatory arthritis like RA in human. In this study, I analyzed seriousness variations and serum biomarkers of RA and IP phenotype in terms of heterogeneous and homogeneous transgene in D1CC mouse. [Results] D1CC carried homogeneous transgene showed severe phenotype in both of RA and IP. [Conclusion] These results were coincident with the similar conclusion from epidemiologic studies in which RA-related major histocompatibility complexes have been analyzed.

### P1-003

#### Effect of CDK6 inhibitor on mice collagen-induced arthritis model

Rie Komatsu<sup>1</sup>, Tomoo Sato<sup>1</sup>, Yoshihisa Yamano<sup>1</sup>, Kazuo Yudoh<sup>1</sup>, Moroe Beppu<sup>2</sup>, Kusuki Nishioka<sup>3</sup>, Toshihiro Nakajima<sup>1,3,4</sup>, Ryoji Fujii<sup>1</sup>

<sup>1</sup>Institute of Medical Science, St. Marianna University School of Medicine, Kawasaki, Japan, <sup>2</sup>Department of Orthopaedic Surgery, St. Marianna University School of Medicine, Kanagawa, Japan, <sup>3</sup>Institute of Medical Science, Tokyo Medical University, Tokyo, Japan, <sup>4</sup>Misato Marine Hospital, Kohchi, Japan

Conflict of interest: None

[Objectives] We previously reported that SPACIA1 is a novel gene associated with abnormal synovial proliferation at G1 phase. We identified CDK6, one of cell cycle regulator genes at G1 phase, which was reduced by half with SPACIA1 siRNA in RASFs. Recently we also reported that CDK6 is functionally involved in synoviocyte proliferation, at least in cultured RASFs. We therefore investigated whether a compound for selective inhibition of CDK6 affect proliferation of RASFs and collagen-induced arthritis (CIA), an animal model of RA. [Methods] We confirmed effects of the compound on CDK6 expression in RASFs using real-time PCR and Western blot analysis. To assess the involvement of CDK6 in RA, the collagen-induced arthritis model was performed with the compound in DBA/1J mice. Arthritis score and histopathological examination were evaluated in those mice. [Results] CDK6 expression was significantly reduced with the compound at both the mRNA and protein levels in RASFs. Furthermore, CIA and characteristic features of pathology in synovial tissues were markedly suppressed in treatment of mice with the compound. [Conclusion] CDK6 may play a crucial role in arthritis. These observations suggest that inhibition of CDK6 has potential for RA treatment.

### P1-004

#### Insulin Suppresses Pro-inflammatory Cytokine Dependent Cartilage Degrading Enzyme Gene Expression in OA and RA Fibroblast-like Synoviocytes

Daisuke Hamada<sup>1</sup>, Ichiro Tonogai<sup>2</sup>, Tomohiro Goto<sup>2</sup>, Koichi Sairyo<sup>2</sup>

<sup>1</sup>Department of Orthopedics, Tokushima University Hospital, Tokushima, Japan, <sup>2</sup>Institute of Health Biosciences, Tokushima University Graduate School, Tokushima, Japan

Conflict of interest: None

[Objectives] The purpose of this study is to demonstrate whether insulin selectively suppresses gene expression of the cartilage degrading enzymes in human FLSs of OA and RA patients, counteracting the effect of TNF $\alpha$  or IL-1 $\beta$ . [Methods] Human FLSs were isolated from the synovial tissues of 7 OA and 7 RA patients undergoing total knee arthroplasty after obtaining informed consent under approval from the IRB. FLSs were serum-starved overnight. Then cells were treated with cytokine and insulin for 24 hr before harvesting. Quantitative real-time PCR was performed using TaqMan probes and Universal Master Mix (Applied Biosystems). Statistical analyses were carried out using Prism, with p<0.05 was considered significant. [Results] Insulin suppressed TNF $\alpha$ -induced MMP1, MMP13 and ADAMTS4 gene expression and IL-1 $\beta$ -induced gene expression of MMP1 and ADAMTS4 in OA and RA groups (p<0.05). The magnitude of suppression in RA group was greater than that in OA groups. Further more IL-6 gene expression was clearly suppressed by insulin in OA and RA groups. [Conclusion] This study demonstrated that insulin regulates catabolic enzyme gene expression in OA and RA FLSs. Insulin may protect cartilage by suppressing TNF $\alpha$  and IL-1 $\beta$  dependent expression of cartilage-degrading enzymes in FLSs.

### P1-005

#### Critical role of Ror1 signaling in MMPs induction in fibroblast-like synoviocytes (FLS) from patients with rheumatoid arthritis (RA)

Kaoru Yamagata, Kazuhisa Nakano, Shingo Nakayamada, Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

Conflict of interest: None

**Objectives:** Wnt5a, highly expressed in RA FLS, binds to Ror2, a receptor tyrosine kinase (RTK), on pre-osteoclasts (pre-OC), resulting in OC differentiation. These results shed the light on the Wnt signaling in the pathogenesis of RA. We here assessed the role of Ror1, the other Ror family RTKs, in FLS. **Methods:** FLS were obtained from patients with RA and OA at total joint replacement. Ror1 expression was evaluated by immunohistochemistry and qPCR. Expression of MMPs in FLS was determined by qPCR. After treatment of FLS with some inhibitors, phosphorylation of signaling molecules and MMP-13 gene expression were

determined by WB and qPCR, respectively. Recruitment of transcriptional factors to *MMP-13* promoter was determined by ChIP. **Results:** *Ror1* was detected in the synovium from OA, but not RA. Stimulation with TNF $\alpha$  significantly decreased *Ror1* mRNA expression in FLS. *MMP-13* expression was enhanced when *Ror1* gene was knocked down by siRNA or FLS were treated with PP2, a c-Src inhibitor and Akt inhibitors. FoxO1 was recruited to *MMP-13* promoter after the treatment of FLS with PP2. **Conclusions:** These data suggest that the decrease of *Ror1* expression in FLS induces MMP-13-mediated cartilage matrix degradation in the pathogenesis of RA.

### P1-006

#### **ABIN (A20-Binding Inhibitors of NF- $\kappa$ B)-3 in a RA-FLS cell line enhances the ubiquitination of Akt**

Hideya Igarashi, Katsuhiko Ishihara

Department of Immunology and Molecular Genetics, Kawasaki Medical School, Okayama, Japan

Conflict of interest: None

[Objectives] To elucidate the molecular function of ABIN-3, a member of ABIN (A20-Binding Inhibitors of NF- $\kappa$ B) family, in RA-FLS, we established and analyzed the stable transfectant of a human RA-FLS cell line MH7A expressing ABIN-3/EGFP fusion protein (designated as A3E). [Methods] The candidate genes influenced by the over-expression of ABIN-3 were identified by DNA-microarray performed between A3E and control transfectant expressing EGFP only. The real-time PCR and western blot assays were conducted to analyze the expression and activation levels of various molecules. [Results] Microarray analysis showed that the transcription of the inflammation-associated genes, matrix metalloproteinase MMP-1 and -3 were down-regulated in A3E. Among the molecules regulating expression of MMPs, the amount of phosphorylated Erk and Akt was reduced. Interestingly, ubiquitination of Akt is enhanced in A3E, suggesting that lower level of phosphorylated Akt might be due to the degradation or functional inactivation by ubiquitination and reduced Akt activity may contribute to the growth inhibition and accelerated cell death shown by A3E. [Conclusion] ABIN-3 may possibly regulate the ubiquitination of Akt, and maintain its expression and activation level to protect the RA-FLS from the cell death.

### P1-007

#### **Contribution of the calcium signaling to TNF $\alpha$ -induced clock gene regulation in rheumatoid synovial cells**

Ayako Nakai<sup>1</sup>, Kohsuke Yoshida<sup>2</sup>, Teppei Hashimoto<sup>3,4</sup>, Nao Shibamura<sup>5</sup>, Kenta Kaneshiro<sup>1</sup>, Naonori Hashimoto<sup>1</sup>, Akira Hashiramoto<sup>2</sup>

<sup>1</sup>Faculty of Health Sciences, Kobe University School of Medicine, Kobe, Japan, <sup>2</sup>Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, <sup>3</sup>Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, <sup>4</sup>Department of Rheumatology, Kobe Kaisei Hospital, Kobe, Japan, <sup>5</sup>Department of Orthopaedic Surgery, Kobe Kaisei Hospital, Kobe, Japan

Conflict of interest: None

[Objectives] We previously showed that TNF $\alpha$  inhibited the expression of Period (*Per2*), a circadian clock gene, via D-box binding protein such as *Dbp* and *E4bp4* in rheumatoid synovial cells. Since a recent report presented a novel cooperation of intra-cellular calcium signaling and *Dbp* expression, we investigated the relationship between the clock gene expression and calcium signaling in TNF $\alpha$ -stimulated synovial cells. [Methods] After incubation with an intracellular [Ca<sup>2+</sup>] chelator BAPTA-AM (25mg/mL) or a calcineurin inhibitor FK-506 (Tacrolimus; up to 25 mg/mL) for 1 hr, synovial cells were stimulated with TNF $\alpha$  for 24 hrs. Then, mRNA expression of *Per2* and *Dbp*, and cell viability were analyzed by real-time PCR and Cell Counting Kit-8, respectively. [Results] The mRNA expression of *Per2* was suppressed by TNF $\alpha$ , which was cancelled by BAPTA-AM, but not FK-506. As well as *Per2*, TNF $\alpha$ -induced *Dbp* suppression was cancelled by BAPTA-AM. The viability of the synovial cells was increased by TNF $\alpha$ , and this was inhibited by treatment with BAPTA-AM. [Conclusion] TNF $\alpha$  modulates the expression of *Dbp* via calcium signaling, thereby inhibits those of *Per2* and cell viabilities, suggesting a novel therapeutic strategy for RA by regulating clock genes.

### P1-008

#### **Immediate early response gene X-1 (IEX-1) is a negative regulator of rheumatoid arthritis synovial fibroblasts**

Akio Morinobu<sup>1</sup>, Keisuke Nishimura<sup>1</sup>, Goichi Kageyama<sup>1</sup>, Jun Saegusa<sup>1,3</sup>, Shunichi Kumagai<sup>2</sup>

<sup>1</sup>Rheumatology, Kobe University Hospital, Kobe, Japan, <sup>2</sup>Center for Thematic Diseases, Shinko Hospital, Kobe, Japan, <sup>3</sup>Clinical Laboratory, Kobe University Hospital

Conflict of interest: Yes

[Objectives] To address the role of immediate early response gene X-1 (IEX-1) in rheumatoid arthritis synovial fibroblasts (RA-SF) [Methods] Synovial fibroblasts from RA and OA patients were cultured in vitro. Protein and mRNA expression were determined by western blotting and quantitative RT-PCR. Cell survival was assayed by WST-8, and apoptosis was detected by a cell death detection ELISA and annexin V staining using a flow cytometer. In some experiments, IEX-1 mRNA was down-regulated by siRNA. IEX-1 protein was stained in surgical specimen of the joint. [Results] Trichostatin A (TSA), a histone deacetylase inhibitor, up-regulated IEX-1. IEX-1 mRNA levels were higher in RA-SF than in OA-SF, and was further up-regulated by TNF $\alpha$  in RA-SF. IEX-1 was also expressed in the pannus of RA patient joints. Knockdown of IEX-1 up-regulated TNF $\alpha$  mRNA expression by LPS, indicating that IEX-1 down-regulates TNF $\alpha$ . Furthermore, knockdown of IEX-1 protected RA-SF from apoptosis induced by TSA and anti-Fas mAb, indicating that IEX-1 is pro-apoptotic in RA-SF. [Conclusion] IEX-1 is over-expressed in RA-SF and induced by TNF $\alpha$ . It suppresses TNF $\alpha$  production and induces apoptosis in RA-SF. Thus IEX-1 seems to negatively regulate RA-SF activation.

### P1-009

#### **Mechanism the efficacy of combination therapy with methotrexate and tacrolimus in rheumatoid arthritis**

Tomohiro Kameda, Hiroaki Dobashi, Risa Wakiya, Hiroki Ozaki, Hiromi Shimada, Shusaku Nakashima, Yohei Takeuchi, Miharu Izumikawa, Kentaro Susaki

Department of Internal Medicine, Division of Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University, Kagawa, Japan

Conflict of interest: None

[Objectives] We reported that the efficacy of combination therapy with methotrexate (MTX) and low dose tacrolimus for MTX refractory rheumatoid arthritis (RA) patients. Additionally, we investigated mechanism that the effectiveness of combination therapy using the human monocytic cell line (THP-1 cells). In this research, we focused the one of the ATP-binding cassette (ABC) transporters, multidrug resistance-associated protein 2 (MRP2), which is pumped out of the cell. We reported that the combination therapy reduce MRP2 expression. We clarify the effect of MRP2 expression for combination therapy with MTX and tacrolimus in synovial cell. [Methods] We examined the MRP2 expression using synovial cells of normal, osteoarthritis and RA. Therefore, we investigate that the effect of MRP2 expression for treatment of MTX alone, tacrolimus alone and combination these two agents. [Results] MRP2 presented on the synovial cells of normal, osteoarthritis and RA. In addition, expression of MRP2 was reduced by combination therapy on RA synovial cell. [Conclusion] We suggest that the MRP2 expression on synovial cells associated with the mechanism of effectiveness by combination therapy for RA patients.

### P1-010

#### **Analysis of effects of salazosulfapyridine using surfaceomics**

Kazuki Omoteyama<sup>1</sup>, Toshiyuki Sato<sup>1</sup>, Mitsumi Arito<sup>1</sup>, Naoya Suematsu<sup>1</sup>, Manae S. Kurokawa<sup>2</sup>, Tomohiro Kato<sup>1</sup>

<sup>1</sup>Clinical Proteomics and Molecular Medicine, St. Marianna University Graduate School of Medicine, Kawasaki, Japan, <sup>2</sup>Disease Biomarker Analysis and Molecular Regulation, St. Marianna University Graduate School of Medicine, Kawasaki, Japan

Conflict of interest: None

[Objectives] Effects of salazosulfapyridine (SASP) on synovial cells are little known. Thereby effects of SASP on a human synovial sarcoma cell line of SW982 were investigated from the viewpoint of cell surface protein profiles (surfaceome). Changes of the surfaceome are expected to affect cell functions. However, there has been no effective and comprehensive method to analyze the surfaceome. Here we applied a recently reported cell surface protein capture technology to the analysis of surfaceome. [Methods] SW982 cells were treated with SASP for 24 h and then surface proteins of the living cells were labeled with biotin. After cell lysis, the biotinylated cell surface proteins were separated by avidin-beads, and then were subjected to 2D-DIGE to detect proteins affected by SASP. [Results] A total of 576 protein spots were visualized by 2D-DIGE. Among them, 1 protein spot showed more than 1.5-fold intensity and 10 protein spots showed less than 1/1.5-fold intensity in the SASP-treated cells compared to the non-treated cells, respectively. Proteins were identified by mass spectrometric analysis, which included VIMENTIN and HSP90B1. [Conclusion] We found that SASP induced surfaceome changing. We will next investigate effects of the surfaceome change on functions of synovial cells.

### P1-011

#### Secretion of inflammatory factors from chondrocytes by layilin signaling

Mitsumi Arito<sup>1</sup>, Manae S. Kurokawa<sup>3</sup>, Kazuki Omoteyama<sup>1</sup>, Kazuo Yudoh<sup>4</sup>, Hiroshi Nakamura<sup>5</sup>, Moroe Beppu<sup>2</sup>, Tomohiro Kato<sup>1</sup>

<sup>1</sup>Clinical Proteomics & Molecular Medicine, St. Marianna University Graduate School of Medicine, <sup>2</sup>Department of Orthopaedic Surgery, St. Marianna University School of Medicine, <sup>3</sup>Disease Biomarker Analysis and Molecular Regulation, St. Marianna University Graduate School of Medicine, <sup>4</sup>Institute of Medical Science, St. Marianna University Graduate School of Medicine, <sup>5</sup>Department of Orthopedic Surgery, Nippon Medical School

Conflict of interest: Yes

[Objectives] Layilin (LAYN), transmembrane protein with a C-type lectin-like domain is known to be a receptor for hyaluronic acid (HA). In rheumatoid arthritis (RA), inflammatory cytokines like tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) have been known to play pathological roles. HA with low molecular weight is speculated to exacerbate inflammation in RA. In this context, differences of quantity and functions of HA receptors would affect the severity of inflammation in RA. However, roles and regulation of LAYN in articular chondrocytes have been poorly understood. Thus, we clarified regulation of LAYN and LAYN-specific roles in chondrocytes. [Methods] We investigated whether TNF- $\alpha$  affected expression levels of LAYN in human articular chondrocytes (n=8) by western blot and whether binding of antibodies to the extracellular domain of LAYN affected secretion of inflammatory cytokines using a chondrosarcoma cells by a cytokine array. [Results] We found that TNF- $\alpha$  up-regulated expression levels of LAYN in the chondrocytes. Further, the LAYN signaling was found to enhance secretion of inflammatory factors, complement5 (C5)/C5a, from the cells. [Conclusion] Our results indicate that LAYN would be involved in the enhancement of inflammation in joint diseases such as RA.

### P1-012

#### Effects of tofacitinib on nucleic acid metabolism in human articular chondrocytes

Mitsumi Arito<sup>1</sup>, Hideki Koizumi<sup>1,2</sup>, Wataru Endo<sup>1,2</sup>, Manae S. Kurokawa<sup>3</sup>, Kazuki Omoteyama<sup>1</sup>, Moroe Beppu<sup>2</sup>, Tomohiro Kato<sup>1</sup>

<sup>1</sup>Clinical Proteomics & Molecular Medicine, St. Marianna University Graduate School of Medicine, <sup>2</sup>Department of Orthopaedic Surgery, St. Marianna University School of Medicine, <sup>3</sup>Disease Biomarker Analysis and Molecular Regulation, St. Marianna University Graduate School of Medicine

Conflict of interest: None

[Objectives] In our previous screening of chondrocyte protein profiles, the amount of adenosine monophosphate deaminase (AMPD) 2 was found probably decreased by tofacitinib, a recently approved oral anti-rheumatic drug. Extending the study, we here confirmed the decrease of

AMPD2 by tofacitinib and further investigated effects of tofacitinib on purine nucleotide metabolism in chondrocytes. [Methods] Human articular chondrocytes and OUMS-27 cells of a human chondrosarcoma cell line were incubated with or without tofacitinib for 48 hours. Then the amounts of AMPD2 and other purine metabolism-related enzymes were investigated by western blot. Also, the amounts of cellular AMP and adenosine were assessed by liquid chromatography-mass spectrometry. [Results] We confirmed the decrease of AMPD2 by tofacitinib (p=0.025) and found that cellular adenosine levels were increased by tofacitinib (p=0.014). AMP levels tended to be increased (p=0.066) and adenosine kinase and 5'-nucleotidase levels tended to be decreased (p=0.067 and p=0.074, respectively) by tofacitinib. [Conclusion] Our data indicate that tofacitinib increases the cellular level of adenosine, which is known to have anti-inflammatory activity, by the down-regulation of AMPD2. This would be a novel functional aspect of tofacitinib.

### P1-013

#### Specifying the autoantibody-inducing CD4 T cell (*ai*CD4 T cell) causing systemic lupus erythematosus (SLE) out of PD-1<sup>+</sup>CD45RB<sup>lo</sup>122<sup>lo</sup> CD4 subpopulation using mass spectrometry

Shunichi Shiozawa, Yumi Miyazaki, Ken Tsumiyama

Department of Medicine, Rheumatic Disease Unit, Kyushu University Beppu Hospital, Beppu, Japan

Conflict of interest: None

[Objectives] We have shown that repeated immunization of mice with antigen reproducibly led to development of SLE, in which a novel T cell type which we term an autoantibody-inducing CD4 T (*ai*CD4 T) cell was generated *via* TCR revision at periphery. The *ai*CD4 T cell induces varieties of autoantibodies and also helps full maturation of CTL to induce lupus tissue injuries. We identified that *ai*CD4 T cell belongs to PD-1<sup>+</sup>CD45RB<sup>lo</sup>122<sup>lo</sup> CD4 T subpopulation, and now tried to further specify the *ai*CD4 T cell by surface markers. [Methods] BALB/c mice were repeatedly immunized with OVA. To isolate *ai*CD4 T cell, we extracted membrane and cytoplasmic fractions of PD-1<sup>+</sup>CD45RB<sup>lo</sup>122<sup>lo</sup> CD4 T subpopulation. They were electrophoresed and protein fractions unique to the PD-1<sup>+</sup>CD45RB<sup>lo</sup>122<sup>lo</sup> CD4 T subpopulation were identified thru mass spectrometry. [Results] Under mass spectrometry, we identified DNA topoisomerase 2-beta (181 kDa), DOCK 8 (238 kDa), VWA5A (87 kDa), STAT5b (89 kDa), epidermal growth factor receptor substrate 15-like 1 (99 kDa), FLAP (18 kDa) as candidates for markers of *ai*CD4 T cell. [Conclusion] The surface markers for *ai*CD4 T cell were specified further out of PD-1<sup>+</sup>CD45RB<sup>lo</sup>122<sup>lo</sup> CD4 T subpopulation.

### P1-014

#### Inhibition of regulatory T cells plasticity to suppress autoimmune symptoms in MRL/lpr mice by the DNA methyltransferase inhibitors azacitidine

Reiko Takahashi<sup>1</sup>, Fumihiko Kimura<sup>2</sup>, Kenji Itoh<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, National Defense Medical College, <sup>2</sup>Division of Hematology, Department of Internal Medicine, National Defense Medical College

Conflict of interest: None

[Objectives] DNA hypomethylation of CD4<sup>+</sup> T lymphocytes has been the important pathogenesis of SLE. On the other hand, MRL/lpr mice with treatment of 5-azacytidine (5AzC) have been reported to live longer. Then, the purpose of this study is to analyze how 5AzC affected MRL/lpr mice. [Methods] MRL/lpr mice or MRL/+ mice were treated twice a week from 4 to 20 weeks with intraperitoneal injections of 50 $\mu$ g of 5AzC, and they were analyzed by flowcytometry. [Results] 5AzC suppressed autoimmune phenotypes in MRL/lpr mice with the improvement of B and T cell phenotypes. Foxp3 expression of MRL/lpr mice was decreased. However, 5AzC increased Foxp3 expressions in MRL/lpr mice. When CD4<sup>+</sup>CD25<sup>bright</sup> cells (i. e. Foxp3<sup>+</sup> cells) were transferred into irradiated syngeneic mice with naive T cells, Foxp3<sup>+</sup> cells from MRL/lpr mice lost suppressive functions, however, those from MRL/lpr mice with 5AzC maintained them. In vitro culture, Foxp3<sup>+</sup> cells from MRL/lpr mice converted to IFN $\gamma$ <sup>+</sup>Foxp3<sup>+</sup> cells (exFoxp3 cells) easily, which means acceleration of regulatory T cells (Treg) plasticity. In MRL/lpr mice with

5AzC, exFoxp3 cells from Foxp3<sup>+</sup> cells were decreased. [Conclusion] Prevention of Treg plasticity by 5AzC is one of the important pathways of ameliorating symptoms of MRL/lpr mice.

### P1-015

#### Analysis of immunocompetent cell and CCR5 in Systemic Lupus Erythematosus

Mie Kitagaichi<sup>1</sup>, Asako Chiba<sup>2</sup>, Shihoko Nakajima<sup>1</sup>, Eri Hayashi<sup>1</sup>, Ken Yamaji<sup>1</sup>, Naoto Tamura<sup>1</sup>, Yoshinari Takasaki<sup>1</sup>, Sachiko Miyake<sup>2</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology Juntendo University School of Medicine, <sup>2</sup>Department of Immunology, Juntendo University School of Medicine

Conflict of interest: None

[Objectives] CCR5 is a chemokine receptor expressed on the surface of monocytes and Th1-polarized T cells. CCR5 is able to bind several ligands such as CCL5/RANTES which induce monocyte migration. We investigate its expression on peripheral blood mononuclear cells (PBMC) in SLE and healthy donors. [Methods] PBMC were separated from SLE patients and sex- age-matched healthy controls (HC) using Lymphoprep and were stained with antibodies against lineage marker and chemokine receptors. The frequency of T cells, B cells, Monocytes (CD14<sup>lo</sup>CD16<sup>+</sup>, CD14<sup>+</sup>CD16<sup>+</sup>, CD14<sup>+</sup>CD16<sup>-</sup> monocytes) NK cells, dendritic cells (myeloid DC, plasmacytoid DC) and their CCR5 expression were analyzed using flowcytometry. [Results] The frequency of monocytes was increased significantly in SLE patients. In contrast, the frequency of myeloid DC and NK cells was reduced in SLE patients. The CCR5 expressing cells were increased among CD14<sup>lo</sup>CD16<sup>+</sup> monocytes and B cells but not CD14<sup>+</sup>CD16<sup>+</sup> and CD14<sup>+</sup>CD16<sup>-</sup> monocytes in SLE patients compare to that in HC. There was positive correlation between disease activity and the frequency of CCR5-positive CD14<sup>lo</sup>CD16<sup>+</sup> monocytes. [Conclusion] These findings suggested that CD14<sup>lo</sup>CD16<sup>+</sup> monocytes play an important role in the pathogenesis of SLE.

### P1-016

#### Involvement of mucosal-associated invariant T cells in the pathogenesis of rheumatoid arthritis and ankylosing spondylitis

Eri Hayashi<sup>1,2</sup>, Asako Chiba<sup>2</sup>, Mie Kitagaichi<sup>1,2</sup>, Shihoko Nakajima<sup>1,2</sup>, Makio Kusaoi<sup>1</sup>, Fumio Sekiya<sup>1</sup>, Kurisu Tada<sup>1</sup>, Michihiro Ogasawara<sup>1</sup>, Ken Yamaji<sup>1</sup>, Naoto Tamura<sup>1</sup>, Yoshinari Takasaki<sup>1</sup>, Sachiko Miyake<sup>2</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan, <sup>2</sup>Department of Immunology, Juntendo University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] Mucosal associated invariant T (MAIT) cells are innate lymphocytes which are restricted by MR1 and express semi-invariant TCR. Previously we have reported that MAIT cells contribute to the arthritic inflammation by using animal models of arthritis. In this study, we investigate whether MAIT cells are involved in the pathogenesis of human inflammatory arthritic diseases including rheumatoid arthritis (RA) and ankylosing spondylitis (AS). [Methods] Peripheral blood mononuclear cells (PBMC) were separated by Lymphoprep and were stained with anti-human monoclonal antibodies. PBMC were stimulated with phorbol-myristate-acetate and ionomycin, and the cytokine production by MAIT cells was examined by intracellular cytokine staining. Cells were analyzed by FACS Fortessa. [Results] MAIT cells are decreased in RA and AS patients. In active RA patients, the expression of CD161 on MAIT cells was reduced and that of CCR9, a gut-tropic receptor, was increased. The frequency of MAIT cells were inversely correlated with the frequency of CCR9<sup>+</sup> cells and IL-17 producing cells in RA. [Conclusion] These findings suggested that MAIT cells might be involved in the pathogenesis of RA.

### P1-017

#### The involvement of innate-like lymphocytes in patients with polymyalgia rheumatica

Shihoko Nakajima<sup>1,2</sup>, Asako Chiba<sup>2</sup>, Eri Hayashi<sup>1,2</sup>, Mie Kitagaichi<sup>1,2</sup>, Makio Kusaoi<sup>1</sup>, Takayuki Kon<sup>1</sup>, Fumio Sekiya<sup>1</sup>, Michihiro Ogasawara<sup>1</sup>,

Ken Yamaji<sup>1</sup>, Naoto Tamura<sup>1</sup>, Yoshinari Takasaki<sup>1</sup>, Sachiko Miyake<sup>2</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan, <sup>2</sup>Department of Immunology, Juntendo University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] Polymyalgia rheumatica (PMR) is a chronic inflammatory disorder of unknown cause in elderly individuals. Although the pathogenesis of PMR is unknown, the increased levels of proinflammatory cytokines such as IL-6, IL-8, IL-1 $\beta$  was demonstrated in serum. Innate-like lymphocytes are important cells to initiate and promote inflammation. The involvement of innate-like lymphocytes in PMR has not studied. [Methods] Peripheral blood mononuclear cells from PMR patients as well as age- and sex-matched healthy controls were isolated from heparinized blood and then stained with combinations of the monoclonal antibodies and CD1d tetramer to investigate innate-like lymphocytes including iNKT cells,  $\gamma\Delta$  T cells, MAIT cells, B-1 cells, NK cells and monocytes, and were analyzed by FACS. Cytokine production was determined by intracellular staining upon activation with PMA and ionomycin. [Results] The frequency of  $\gamma\Delta$  T cells was reduced and the expression of CD161, linked to IL-17 production was up-regulated on  $\gamma\Delta$  T cells and MAIT cells in PMR patients. Furthermore, the level of CD161 was up-regulated on CD4<sup>+</sup> T cells and cytokine responses were shifted toward Th17 cells in PMR patients. [Conclusion] These findings suggested the involvement of innate-like lymphocytes in the inflammation of PMR.

### P1-018

#### The reduction of serum uric acid level might prevent atherosclerosis in mice

Yoshitaka Kimura<sup>1,2</sup>, Tamiko Yanagida<sup>1</sup>, Akiko Onda<sup>1</sup>, Maki Takayama<sup>1</sup>, Kurumi Asako<sup>1</sup>, Akiko Okamoto<sup>1</sup>, Hiroto Kikuchi<sup>1</sup>, Toshihiro Nanki<sup>3</sup>, Hajime Kono<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Teikyo University of Medicine, Tokyo, Japan, <sup>2</sup>Department of Allergy and Rheumatology, The University of Tokyo, Tokyo, Japan, <sup>3</sup>Teikyo Academic Reserch Center, Teikyo University of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] Using the transgenic mice expressed uricase, an uric acid hydrolytic enzyme, we investigated the reduction of serum uric acid level could prevent atherosclerosis in mice. [Methods] We prepared uricase transgenic mice based in C57BL/6 mice and bred them with LDLR<sup>-/-</sup> mice and ApoE<sup>-/-</sup> mice. LDLR<sup>-/-</sup>Uricase<sup>Tg</sup> mice, ApoE<sup>-/-</sup>Uricase<sup>Tg</sup> mice and control mice (LDLR<sup>-/-</sup> mice and ApoE<sup>-/-</sup> mice) at 6 weeks of age received high-fat diet for 16 weeks. Aortic sinuses of them were fixed and sliced, and these slides were stained with hematoxylin-eosin. We measured atherosclerosis area of these slide and computed volume of lesions. Aortas were stained with oil red O and measured area of atherosclerosis lesions. [Results] The volumes of atherosclerosis lesions in aortic sinuses of LDLR<sup>-/-</sup>Uricase<sup>Tg</sup> (0.158 $\pm$ 0.016 mm<sup>3</sup>) [n=17] were smaller than that of LDLR<sup>-/-</sup> (0.231 $\pm$ 0.017 mm<sup>3</sup>) [n=12] [p=0.0049]. There were no significant differences between ApoE<sup>-/-</sup>Uricase<sup>Tg</sup> (0.227 $\pm$ 0.022 mm<sup>3</sup>) [n=15] and ApoE<sup>-/-</sup> (0.292 $\pm$ 0.032 mm<sup>3</sup>) [n=7] [p=0.11]. In the ratio of area of atherosclerosis in aorta, there were little differences between each group. [Conclusion] It was showed that the reduction of serum uric acid level may inhibit the progression of atherosclerosis in uricase transgenic mice.

### P1-019

#### T-bet regulates differentiation of Foxp3 expression in programmed cell death-1-deficient mice

Masahiro Tahara<sup>1</sup>, Yuya Kondo<sup>1</sup>, Masahiro Yokosawa<sup>1</sup>, Shunta Kaneko<sup>1</sup>, Hiroto Tsuboi<sup>1</sup>, Satoru Takahashi<sup>2,3</sup>, Isao Matsumoto<sup>1</sup>, Takayuki Sumida<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, <sup>2</sup>Departments of Anatomy and Embryology, Faculty of Medicine, University of Tsukuba, <sup>3</sup>Laboratory Animal Resource Center, University of Tsukuba

Conflict of interest: None

[Objective] To clarify the role of PD-1 in the differentiation of CD4<sup>+</sup>



T cells and pathological condition [Methods] PD-1 deficient T-bet transgenic (Tg) mice (P/T) were generated by crossing T cell specific T-bet Tg mice with PD-1 KO mice. 1) Phenotype was examined in P/T. 2) The pathological evaluation of several organs was performed. 3) Cytokine production and transcription factor expression in splenic CD4<sup>+</sup> T cells were analyzed by FACS. 4) CD4<sup>+</sup> T cells were cultured in the condition in favor of Foxp3<sup>+</sup>Treg differentiation. 5) Splenocytes isolated from P/T were transferred into Rag-2 KO mice. [Results] 1) P/T showed growth retardation and died within 10 weeks. 2) Histological examination revealed the infiltration of inflammatory cells in liver, pancreas, and intestine. 3) FACS analysis showed high production of IFN- $\gamma$  and significant reduction of Foxp3<sup>+</sup>Treg cells in P/T. 4) CD4<sup>+</sup> T cells did not differentiate to Foxp3<sup>+</sup> Tregs in P/T. 5) The infiltration of mononuclear cells were observed in organs similar to P/T in recipient Rag-2 KO mice. [Conclusion] Systemic inflammation and short-life span in P/T might be induced by the augmented Th1 response and the reduced Foxp3<sup>+</sup> Treg cells by trigger of PD-1-deficient.

### P1-020

#### The dynamism of bone marrow cells in CIA mice after bone marrow transplantation from GFP transgenic mice

Miwa Uzuki<sup>1,2,3,4</sup>, Takashi Sawai<sup>3,4</sup>

<sup>1</sup>Department of Pathology, Iwate Medical University, School of Medicine, Morioka, Japan, <sup>2</sup>Faculty of Medical Science and Welfare, Tohoku Bunka Gakuen University, <sup>3</sup>Department of Pathology, Tohoku University, Graduate School of Medicine, <sup>4</sup>Division of Pathology, Sendai Open Hospital

Conflict of interest: None

[Objectives] We can discriminate between the donor cells and recipient cells by using GFP transgenic mice. We examine the dynamics of bone marrow origin cells in arthritis. [Methods] After irradiation, C57/B6 mice under myelosuppression state got bone marrow transplantation. Type II collagen induced arthritis (CIA) was made after GFP bone marrow cells engraftment. We examined fluorescent specimen by using digital microscopical method (NanoZoomer, Hamamatsu Photonics). [Results] The bone marrow origin cells with GFP were found in inflammatory synovial tissue and pannus. These cells were morphologically granulocytes, macrophages or fibroblast like cells (FLC). In FLC, CD14, CD34 and MMP-3 were positive. [Conclusion] FLC of bone marrow origin were found in arthritic lesion in CIA mice. These cells may contribute to the onset of arthritis not only in CIA but also in human RA.

### P1-021

#### The role of *Bombina variegata* peptide8/Prokineticin2 in arthritis

Haruyasu Ito, Ken Yoshida, Kentaro Noda, Daitaro Kurosaka  
Division of Rheumatology, Department of Internal Medicine, Jikei University School of Medicine

Conflict of interest: None

**Objective:** We have previously showed that *Bombina variegata* peptide8/Prokineticin2 (Bv8/Prok2) was highly expressed in the synovial tissue of collagen induced arthritis (CIA) mice. However, it is still unknown whether Bv8/Prok2 can induce arthritis. Therefore, we examined whether Bv8/Prok2 recruits polymorphonuclear neutrophils (PMNs) and monocytes *in vitro* and induces inflammatory arthritis *in vivo*. **Methods:** We performed chemotaxis assays for PMNs and monocytes in response to recombinant Bv8/Prok2 (rBv8/Prok2). To determine inflammatory activity of Bv8/Prok2 *in vivo*, we injected PBS or rBv8/Prok2 into knee joints. Immunohistochemical stainings for PMNs (Gr-1/Ly6G) and monocytes (F4/80) were performed to quantify the number of Gr-1/Ly6G and F4/80 positive cells in the Bv8/Prok2 group compared to the PBS group. **Results:** Chemotaxis assays showed that rBv8/Prok2 had recruited PMNs. Gr-1/Ly6G positive cells infiltrating in mouse synovial tissue were significantly higher in the rBv8/Prok2 group compared to the PBS group. There was no significant difference in the number of F4/80 positive cells between both groups. **Conclusions:** Bv8/Prok2 recruited PMNs *in vitro* and induced neutrophil-driven inflammatory arthritis.

### P1-022

#### Human Osteoclasts are Mobilized in Erosive Arthritis of Epstein-Barr Virus-infected Humanized NOD/Shi-*scid*/IL-2R $\gamma^{\text{null}}$ Mice

Yosuke Nagasawa<sup>1</sup>, Natsumi Ikumi<sup>1</sup>, Takamasa Nozaki<sup>1</sup>, Hirotake Inomata<sup>1</sup>, Noboru Kitamura<sup>1</sup>, Mitsuhiro Iwata<sup>1</sup>, Masami Takei<sup>1</sup>

<sup>1</sup>Division of Hematology and Rheumatology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan, <sup>2</sup>Department of Infectious Diseases, National Research Institute for Child Health and Development, Tokyo, Japan

Conflict of interest: None

[Objectives] We previously reported EBV infection induces erosive arthritis in humanized NOG mice. However, the mechanisms are unknown. In this model, multinucleated cells are observed during bone erosion. To determine whether human immune system activates bone erosion, we analyzed the origin of osteoclasts. [Methods] NOG mice (immunodeficient mice) were intravenously injected with human CD34<sup>+</sup> cells (Lonza). Characterization of human hematoimmune system reconstitution was performed. They were intravenously infected with EBV. After 8-10 weeks of infection, they were sacrificed. Sections of their joint tissue were subjected for HE, TRAP and human cathepsin K (specific to humans and dogs) staining. To let osteoclasts differentiate with progenitor cells, their bone marrow cells were cultured with human RANKL and M-CSF. Stimulated cells were stained for TRAP and cathepsin K. [Results] Multinucleated cells present in the bone erosion zone were positive for TRAP and cathepsin K staining. Multinucleated cells were observed among cultured bone marrow cells stimulated with RANKL and M-CSF. TRAP and cathepsin K staining were positive in these multinucleated cells. [Conclusion] Osteoclasts present in the bone erosion zone were human osteoclasts and originated from bone marrow progenitor cells.

### P1-023

#### SH3BP2 gain-of-function mutation exacerbates inflammation and bone loss in a murine collagen-induced arthritis model

Tomoyuki Mukai<sup>1,2</sup>, Keiichiro Nishida<sup>3,4</sup>, Yoshitaka Morita<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Kawasaki Medical School, Kurashiki, Japan, <sup>2</sup>Department of Oral and Craniofacial Sciences, School of Dentistry, University of Missouri-Kansas City, Kansas City, USA, <sup>3</sup>Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, <sup>4</sup>Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Conflict of interest: None

[Objective] SH3BP2 is an adapter protein which regulates immune and skeletal systems. Gain-of-function mutations in SH3BP2 cause cherubism, characterized by jawbone destruction. This study was aimed to examine the role of SH3BP2 in inflammatory bone loss using a collagen-induced arthritis (CIA) model. [Methods] CIA was induced in wild-type and P416R SH3BP2 cherubism mutant knock-in heterozygous (Sh3bp2<sup>KI/+</sup>) mice, an SH3BP2 gain-of-function model. Inflammation and bone loss were examined by clinical inspection and histological and micro-CT analyses. Anti-type II collagen (CII) antibody levels and lymph node cell responses to CII were determined. Macrophage activation and osteoclastogenesis were evaluated in bone marrow macrophages (BMMs). [Results] Sh3bp2<sup>KI/+</sup> mice exhibited more severe inflammation and bone loss with an increased number of osteoclasts. T-cell responses in lymph nodes and serum anti-CII antibody levels were comparable between the genotypes. TNF production and osteoclast differentiation were enhanced in Sh3bp2<sup>KI/+</sup> BMMs. [Conclusion] SH3BP2 gain-of-function augments inflammation and bone loss via increased macrophage activation and osteoclast formation. Therefore, modulation of the SH3BP2 expression may have therapeutic potential for the treatment of arthritis.

### P1-024

#### The effect of anti-IL-6 receptor antibody on cartilage destruction in arthritis mice

Miho Suzuki, Hiroto Yoshida, Keisuke Tanaka, Misato Hashizume, Yoshihiro Matsumoto

Product Research Department, Chugai Pharmaceutical Co., Ltd., Gotem-

ba, Japan

Conflict of interest: None

[Objectives] It has been reported that anti-IL-6 receptor antibody (anti-IL-6R), tocilizumab, inhibits not only bone erosion but also joint space narrowing in clinical trials for RA. The increased expression of cartilage matrix degrading enzyme is thought as playing a role in cartilage destruction. We investigated the effect of anti-IL-6R on cartilage destruction and the increased expression of cartilage matrix degrading enzyme in arthritic mice. [Methods] To prepare a CIA model, mice were immunized intradermally with bovine type II collagen twice on Day 0 and 21. Arthritic mice were intraperitoneally treated with 8 mg of anti-mouse IL-6R (MR16-1) twice on Day 0 and 21. The joint space narrowing of hind limbs on Day 35 was analysed by  $\mu$ CT. The expressions of cartilage matrix degrading enzyme (MMP-3, MMP-13, ADAMTS4 and ADAMTS5) in synovium of hind limbs were analysed by real-time PCR. [Results] MR16-1 suppressed the progression of both arthritis score and joint space narrowing on Day35. Furthermore, MR16-1 inhibited the increased expressions of MMP-3, MMP-13, ADAMTS4 and ADAMTS5 in arthritic mice. [Conclusion] These results suggest that anti-IL-6R suppresses the cartilage destruction via inhibition of the increased expression of cartilage matrix degrading enzyme.

### P1-025

#### Cytokine profile of monozygotic twins with antiphospholipid syndrome (APS) onset at early infancy

Shingo Yamanishi, Toru Igarashi, Yujiro Tanabe, Hikaru Takeshita, Yusuke Ozaki, Yasuhiko Itoh  
Nippon Medical School Hospital, Tokyo, Japan

Conflict of interest: None

[Introduction] Mechanism of thrombosis in APS is unclear. Previous studies revealed that antiphospholipid antibodies (Abs) induced the activation of monocytes (Mo) and vascular endothelium cells (VEC). There are few reports describing cytokine profile (CP) in APS. We studied CP in a case of monozygotic twins with APS. [Case] The twins developed purpura and skin ulcer at early infancy. Skin biopsy revealed capillary thrombus, and anticardiolipin Ab and anti PS/PT Ab were detected. Consequently, they were diagnosed of APS. [Methods] We measured CP in their serum obtained at with symptom and no symptom using Bio-Plex system. [Results] CPs look similar between them with no symptom. IL-8, IL-18, MCP-1, MIP1a, MIP1b, sVCAM-1 and sICAM-1 were elevated in the twins compared with control. Regarding the later-born in the twins, IL-1 $\beta$ , IL-6, IFN $\gamma$  and TNF $\alpha$  were elevated at EBV infection when she developed purpura, compared with no symptom. [Conclusions] Several elevated cytokines in the twins are considered to be derived from Mo and VCE, suggesting that those cells are involved in the pathology of APS. All cytokines except IL-6 elevated at EBV infection in the twin, are not elevated in other cases with EBV infection, suggesting they are distinct and may possibly involve in induction of purpura.

### P1-026

#### Type 2 TNF $\alpha$ receptor (TNFR2) transmits caspase-dependent apoptotic signals in fibroblast-like synoviocyte (FLS) derived from RA

Hiroyasu Hirano<sup>1,2</sup>, Hideya Igarashi<sup>1</sup>, Ayano Yahagi<sup>1</sup>, Yoshitaka Morita<sup>2</sup>, Katsuhiko Ishihara<sup>1</sup>

<sup>1</sup>Department of Immunology and Molecular Genetics, Kawasaki Medical School, Okayama, Japan, <sup>2</sup>Department of Rheumatology, Kawasaki Medical School, Okayama, Japan

Conflict of interest: None

[Objectives] We have found that RA-FLSs express not only TNFR1, but also TNFR2 that is believed to be expressed selectively by hematopoietic cells. To clarify the functional roles for TNFR2 on RA-FLS, we established and analyzed the RA-FLS cell line, MH7A over-expressing TNFR2. [Methods] The expression of each molecule was evaluated by real-time PCR and western blotting. The apoptotic cells were estimated by annexin V staining with FACS. The growth of cells was measured by MTT assay [Results] TNF $\alpha$  inhibited the growth of the transfectant and

induced apoptosis. Since TNFR2 lacks death domain, we first tested a mechanism called "ligand passing" in which TNF $\alpha$  first captured by TNFR2 are transferred to TNFR1, leading to apoptosis through death domain. This possibility was unlikely because apoptosis was not inhibited by anti-TNFR2 mAb 80M2 that stabilizes the binding of TNF $\alpha$  with TNFR2. On the other hand, apoptosis was enhanced when we stimulated the transfectant with the agonistic anti-TNFR2 antibody in the presence of anti-TNFR1 antibody blocking ligand binding, confirming that apoptosis was induced through TNFR2. Furthermore, rapid decrease of TRAF2 and cleavage of caspase-8 and -3 were observed [Conclusion] These data suggest the presence of a novel apoptotic signaling pathway from TNFR2

### P1-027

#### Inflammatory cytokines upregulate anticoagulant factors in the heart of transgenic mice with heart-specific overexpression of TNF- $\alpha$

Yoshihiro Higuchi, Makiko Maekawa, Yasutaka Kimoto, Hideaki Goda, Yoshiyuki Arita, Takahiko Horiuchi

Department of Internal Medicine, Kyushu University Beppu Hospital, Oita, Japan

Conflict of interest: None

[Objectives] The natural anticoagulation systems in the inflammatory site have not been studied. Recent experimental and clinical data have indicated that not only the thrombomodulin (TM)/protein C (PC) pathway but also the protein S (PS)/tissue factor pathway inhibitor (TFPI) system function as potent natural anticoagulants. [Methods] We measured the expression of these anticoagulant factors by RT-PCR and/or Western blot analysis in the heart of transgenic (TG) mice with heart-specific overexpression of TNF- $\alpha$ . [Results] Both procoagulant (tissue factor and plasminogen activator inhibitor 1) and anticoagulant (PS and TFPI) factors were upregulated in the myocardium of 24-wk-old TG but not in that of 4-wk-old TG compared with the wild-type mice. The expression of TM was downregulated in the TG heart, and PC was not detected in the hearts. The transcript levels of PS orphan receptors, Mer and Tyro3, but not Axl, were significantly upregulated in the TG heart. Double immunohistochemical staining revealed that myocardial infiltrating CD3-positive T cells may produce PS in the TG myocardium. [Conclusion] The PS/TFPI was upregulated in the inflammatory myocardium, suggesting a role for the PS/TFPI system in the protection of the heart under both inflammatory and hypercoagulable states.

### P1-028

#### Reduction of Serum ADAM17 Level Accompanied with Decreased Cytokines after Abatacept Therapy in Patients with Rheumatoid Arthritis

Masayu Umemura<sup>1</sup>, Takeo Isozaki<sup>1</sup>, Sho Ishii<sup>1</sup>, Shinya Seki<sup>1</sup>, Nao Oguro<sup>1</sup>, Yoko Miura<sup>1</sup>, Yusuke Miwa<sup>1</sup>, Masanori Nakamura<sup>2</sup>, Katsunori Inagaki<sup>2</sup>, Tsuyoshi Kasama<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan, <sup>2</sup>Division of Orthopaedic Surgery, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] A disintegrin and metalloprotease 17 (ADAM17) appears to be recognized as an important player in tissue destruction and also increased activities. To examine the modulation of serum levels of ADAM17 and inflammatory cytokines in patients with rheumatoid arthritis (RA) in response to therapy of abatacept (ABT). [Methods] Twenty four patients with RA were enrolled in our study. Serum was collected immediately prior to (baseline) and 24 weeks after starting ABT therapy. Serum levels of ADAM17 and cytokines/chemokine were quantified using enzyme-linked immunosorbent assay. [Results] ADAM17 level was markedly higher in RA patients than in healthy individuals. There was a significant overall reduction of RA disease activity (Disease Activity Score 28) from 4.73 to 2.79 after 24 weeks after the ABT therapy. Furthermore, there was a significant reduction in serum level of ADAM17 in RA patients, and the patients achieved clinical responses, and also clinical remission had a significant decrease in ADAM17 level and also levels of tumor necrosis factor  $\alpha$ , IL-6 and CX3CL1 after 24 weeks of ABT

therapy. [Conclusion] Our results suggest that the suppression of ADAM17 secretion and function seems to be a crucial therapeutic target in the treatment of ABT in patients with RA.

### P1-029

#### Long-term chronologic evaluation using power Doppler ultrasonography in patients with rheumatoid arthritis receiving etanercept

Hiroaki Taguchi, Takeo Kudo, Toshihiro Tono, Yasuo Osone, Yutaka Okano, Satoshi Akizuki

Division of Rheumatology, Kawasaki Municipal Kawasaki Hospital, Kawasaki, Japan

Conflict of interest: None

[Objectives] We investigated the association of power Doppler ultrasonography (PDUS) findings with clinical disease activity in patients with rheumatoid arthritis (RA) receiving etanercept (ETA). [Methods] 10 RA patients receiving ETA were included. At 0, 12, and 24 months of ETA therapy, bilateral proximal interphalangeal, interphalangeal, metacarpophalangeal, and wrist joints in each patient were assessed on a 0–3 point scale using PDUS (sum designated as PD22 score). Clinical disease activity was evaluated using Simple Disease Activity Index (SDAI). [Results] Analyses of  $\Delta$ PD22 score and  $\Delta$ SDAI at 12 and 24 months of ETA therapy revealed high correlation coefficients of 0.76 and 0.81, respectively. With SDAI, significant improvement was seen at 12 ( $p < 0.001$ ) but not 24 ( $p = 0.40$ ) months. PD22 score were 11.1, 3.0, and 1.0 at 0, 12, and 24 months, respectively; significant improvement was seen at both 12 ( $p = 0.003$ ) and 24 ( $p = 0.017$ ) months. Clinical remission was observed in 50% of patients both at 12 and 24 months, while sonographic remission was seen in 20% and 40%, respectively. [Conclusion] There was a strong correlation between  $\Delta$ PD22 score and  $\Delta$ SDAI. SDAI did not improve past 12 months, while PD22 score improved until 24 months.

### P1-030

#### Comparison of MRI findings in RA patients treated with biological DMARDs: IFX vs TCZ vs ABT

Tomoya Hirota, Takeshi Suzuki, Hiroshi Ogishima, Shinya Hagiwara, Mizuki Yagishita, Hidenori Takahashi, Izumi Kurata, Saori Abe, Hiroshi Ebe, Hiroyuki Takahashi, Masahiro Yokosawa, Naoto Umeda, Yuya Kondo, Hiroto Tsuboi, Isao Matsumoto, Takayuki Sumida  
Department of Internal Medicine, Faculty of Medicine, University of Tsukuba

Conflict of interest: Yes

[Objectives] To compare MRI findings in RA patients treated with biologic DMARDs. [Methods] 43 RA patients treated with biologic DMARDs (13 to IFX, 15 to TCZ, 15 to ABT) were included. They were evaluated using SDAI and low-field extremity MRI. [Results] 1) SDAI scores were improved by 24 weeks in all groups ( $P < 0.01$ ). 2) Synovitis scores were significantly decreased by 24 weeks in all groups ( $P < 0.05$ ). 3) Significant improvement of bone marrow edema (BME) scores showed from baseline to 24 weeks in IFX and ABT groups (IFX:  $4.52 \pm 4.61$  to  $2.02 \pm 3.32$ ,  $P < 0.05$ ; ABT:  $4.73 \pm 6.49$  to  $1.52 \pm 2.26$ ,  $P < 0.05$ ), in contrast, from 24 weeks to 52 weeks in TCZ group (TCZ:  $8.08 \pm 9.64$  to  $4.75 \pm 7.62$ ,  $P < 0.01$ ). 4) No significant change was found in erosion score. 5) Significant correlations were found between synovitis score at baseline and SDAI at 24 weeks (IFX:  $R = 0.58$ ,  $P < 0.05$ ; TCZ:  $R = 0.60$ ,  $P < 0.05$ ; ABT:  $R = 0.57$ ,  $P < 0.05$ ), additionally, between synovitis score at 24 weeks and SDAI at 52 weeks (IFX:  $R = 0.58$ ,  $P < 0.05$ ; TCZ:  $R = 0.63$ ,  $P < 0.05$ ; ABT:  $R = 0.62$ ,  $P < 0.05$ ). 6)  $\Delta$ SDAI showed no correlations with  $\Delta$ synovitis,  $\Delta$ BME and  $\Delta$ erosion score. [Conclusion] The effect on local regions by TCZ expressed more slowly than IFX and ABT. MRI-detected synovitis may predict SDAI at the 24 weeks later.

### P1-031

#### Modification of quantitative synovial vascularity for rheumatoid finger joint

Jun Fukae, Fumihiko Sakamoto, Akihiro Narita, Mihoko Henmi, Akemi Kitano, Yuko Aoki, Hisanori Takamatsu, Masato Isobe, Masato Shimizu, Megumi Matsuhashi, Takeya Ito, Akio Mitsuzaki, Kazuhide Tanimura

Hokkaido Medical Center for Rheumatic Diseases

Conflict of interest: None

[Objectives] We have established quantitative measurement of synovial vascularity for finger joint and studied change in synovitis in patient with rheumatoid arthritis. Although the method was useful for investigation of synovitis, it required limited medical research environment to obtain reliable results. To use the method in multi-center study, reproducibility of the test needs to be established. [Methods] Finger joints in RA were studied. Sonographic machines (Aplio300 (TOSHIBA), LOGIQe (GE), Avius (HITACHI)) were used. Synovial vascularity was output as area, not pixel dots which depended on each machine. Synovial vascularity was measured by free hand tool or automatic software. [Results] Data among free hand measurements of three sonographers, data between free hand and automatic measurement in one machine and data among automatic measurement of three machines were significantly correlated respectively. [Conclusion] Quantitative method reproducibly output area of synovial vascularity in different sonographers and machines.

### P1-032

#### The comparison of the ultrasonographic improvements in hands of patients with rheumatoid arthritis after treatment of infliximab, tocilizumab and abatacept

Hiroshi Ogishima, Yuya Kondo, Hiroto Tsuboi, Hidenori Takahashi, Mizuki Yagishita, Izumi Kurata, Saori Abe, Hiroshi Ebe, Hiroyuki Takahashi, Chihiro Hagiya, Hiromitsu Asashima, Masahiro Yokosawa, Shinya Hagiwara, Tomoya Hirota, Naoto Umeda, Takeshi Suzuki, Isao Matsumoto, Takayuki Sumida

Department of Internal Medicine, Faculty of Medicine, University of Tsukuba

Conflict of interest: None

[Objectives] To compare the ultrasonographic improvements in patients with RA treated with IFX, TCZ and ABT. [Methods] 1) The patients who had been examined by ultrasonography (US) before the first infusion of IFX, TCZ or ABT from 2010 to 2013 and six months later were extracted electronically from the database of University of Tsukuba hospital. 2) Bilateral first IP joints, second to fifth PIP joints, first to fifth MCP joints and wrists were examined by US. 3) CDAI, the sum of GS score of the 22 joints (GS), that of PD score of the 22 joints (PD) and the differences ( $\Delta$ ) of each score before the first infusion and six month later were compared between IFX, TCZ and ABT. [Results] 1) CDAI before the first infusion of IFX, TCZ and ABT were  $16.8 \pm 5.7$ ,  $15.9 \pm 6.4$ ,  $14.2 \pm 9.7$ ;  $\Delta$ CDAI were  $-10.8 \pm 7.6$ ,  $-11.5 \pm 6.7$  and  $-10.0 \pm 7.4$ ; respectively. As for CDAI and  $\Delta$ CDAI, there were no significant differences between IFX, TCZ and ABT. 2)  $\Delta$ GS were  $-3.1 \pm 10.8$ ,  $-8.1 \pm 16.2$  and  $3.5 \pm 16.4$ .  $\Delta$ GS of TCZ were larger than those of ABT significantly ( $p = 0.03$ ). As for GS, PD and  $\Delta$ PD, there were no significant differences. [Conclusion] As for CDAI,  $\Delta$ CDAI, GS, PD and  $\Delta$ PD, there were no significant differences. In contrast,  $\Delta$ GS of TCZ were larger than those of ABT significantly.

### P1-033

#### Prospective study of Remission Inducing & Maintaining using Ultrasonography in Rheumatoid Arthritis

Kazutoshi Aoki<sup>1</sup>, Yoshiaki Kuga<sup>3</sup>, Michihito Sato<sup>1</sup>, Koji Nishimura<sup>1</sup>, Akiko Shibata<sup>2</sup>, Ryota Sakai<sup>2</sup>, Kentaro Chino<sup>2</sup>, Tsuneo Kondo<sup>2</sup>, Ayumi Okuyama<sup>2</sup>, Hirofumi Takei<sup>2</sup>, Hayato Nagasawa<sup>2</sup>, Shino Takatori<sup>3</sup>, Takuma Wada<sup>4</sup>, Hiroshi Matsuoka<sup>5</sup>, Junji Hayashi<sup>6</sup>, Motohide Kaneko<sup>7</sup>, Kenji Takagi<sup>5</sup>, Toshihide Mimura<sup>4</sup>, Koichi Amano<sup>2</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Saitama Medical Center, Japan Community Health Care Organization, Saitama, Japan, <sup>2</sup>Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan, <sup>3</sup>Orthopedic Surgery, Internaldepartment, Wakaba Hospital, sakado, Japan, <sup>4</sup>Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Moroyama, Japan, <sup>5</sup>Division of Rheumatology and Clinical Immunology, Higashi-Omiya General Hospital, Saitama, Japan, <sup>6</sup>Orthopedic Surgery, Niizashi Central General Hospital, Niiza, Japan, <sup>7</sup>Kaneko Clinic, Kawaguchi, Ja-

pan

Conflict of interest: None

[Objectives] The usefulness of the disease evaluation by a joint echo is shown. The echo remission used as the predictive factor of destructive control of a bone and a joint is defined. [Methods] The cases are diagnosed by RA diagnostic criteria of ACR 2010 at the time of ADA start and are examples of DAS28-ESR > 3.2. In addition, it is necessary for those cases to maintain low disease activity for six months. The change of the MTX dose accepted less than 2 mg/week for three months and the change within 2 mg/week accepted it after registration. The glucocorticoid dose limited it to cases less than 5 mg/day. DMARDs (except MTX) decided not to change it after registration. (PRIMULA: Prospective study of Remission Inducing & Maintaining using Ultrasonography in Rheumatoid Arthritis) [Results] ADA-free group were 13 cases and ADA continuation group nine were registered. There was no difference in contraction of a disease period and the MTX dose between a group. DAS28-ESR of ADA-free group and the continuation group did not have the significant difference in 2.0+0.9, 2.7+0.9 each. Three cases recurred in the ADA-free group. [Conclusion] After having canceled ADA in the joint echo signal score high price example, there were cases that became high in activity.

### P1-034

#### Role of ultrasonographic examination of rheumatoid arthritis patients in daily clinical practice

Hideshi Yamazaki, Yu Funakubo, Tetsuo Takanashi  
Arthritis and Lupus Center, Marunouchi Hospital, Matsumoto, Japan

Conflict of interest: None

[Objectives] Ultrasonography is being applied to analysis of rheumatoid arthritis (RA). The objective of this study was to investigate the role of ultrasonographic examination of rheumatoid arthritis patients in daily clinical practice. [Methods] Three hundred thirty four patients with RA were examined by ultrasonography from February 2013 to January 2014. The study included 187 patients with power Doppler signal (PD) synovitis over grade 2. The patients were evaluated for disease activity according to the Disease Activity Score in 28 joints (DAS28) and treatment of RA. [Results] The percentages of patients with PD synovitis over grade 2 were 37.8% of DAS28 remission, 52% of low disease activity, 74.5% of moderate disease activity, 85.3% of high disease activity. In the 187 patients with PD synovitis over grade 2, 110 patients were not changed the medication, 77 patients were corrected the medication. Eleven patients were corrected the medication in 56 patients who achieved clinical remission with PD synovitis over grade 2. [Conclusion] Ultrasonographic examination of rheumatoid arthritis patients is useful in daily clinical practice.

### P1-035

#### MRI findings of rheumatoid arthritis patients after maintaining biologic-free status for 2 years

Yasuhiro Kubota<sup>1,2</sup>, Nobuo Matsui<sup>2</sup>, Masafumi Ohtani<sup>2</sup>  
<sup>1</sup>Kubota Orthopedics and Rheumatology Clinic, Toyota, Japan, <sup>2</sup>Nagoya City Rehabilitation Center Hospital, Nagoya, Japan

Conflict of interest: None

[Objective] To investigate MRI findings of long-term bio-free RA patients. [Subjects] Subjects were 4 RA patients who were bio-free for ≥2 years following remission. [Method] MRI was performed at the beginning and 1 and 2 years after the introduction of bio-free. Synovitis and bone edema were scored using the RAMRIS. [Results] In case1, synovitis scores were 3 at the beginning of bio-free, 4 after 1 year, and 1 after 2 years; edema scores were 1 at the beginning, 0 after 1 year, and 0 after 2 years. In case2, synovitis scores were 2 at the beginning, 5 after 1 year, and 8 after 2 years; edema scores were 7 at the beginning, 8 after 1 year, and 12 after 2 years. In case3, synovitis scores were 3 at the beginning, and 3 after 1 and 2 years; edema scores were 10 at the beginning, 11 after 1 year, and 8 after 2 years. In case4, synovitis scores were 0 at the beginning, 1 after 1 year, and 0 after 2 years; edema scores were 1 at the begin-

ning, 2 after 1 year, and 1 after 2 years. Case2 showed a gradual increase in synovitis scores, and resumed use of biologics 32 months after stopping biologics. [Conclusion] The scores of edema as well as synovitis must be low at the time of bio-free introduction to maintain bio-free remission.

### P1-036

#### Follow Up for the finger arthritis or rtifness by ultrasound device

Yasuhiro Tani, Noriyuki Miyazaki  
Nagato General Hospital

Conflict of interest: None

[Objectives] To examine for the patients of undifferentiated arthritis which having the joint arthriis or joint pain or joint stiffness. [Methods] Follow up for the patients of the undifferentiated arthritis to check with using ultrasound device by 3 month. There are 33 cases (men 6, women 11), age 57.1, seronegative 28cases and seropositive 5cases. We check the joint and tendon and tendon sheath (PIP joint, MPjoint, wrist joint). [Results] Improvement 11 cases, Osteoarthritis 11 cases, inflammation of the tendon sheath 4 cases, Undifferentiated 7cases. It is not observed for development to the rheumatoid arthritis [Conclusion] It is very important to the check with using the ultrasound device for undifferentiated arthritis.

### P1-037

#### Active synovitis detected by musculoskeletal ultrasound is directly associated with radiographic damage in Rheumatoid Arthritis

Mariko Taira<sup>1</sup>, Tomoko Sugiura<sup>1,2</sup>  
<sup>1</sup>Sugiura Clinic, <sup>2</sup>Institute of Biochemistry, Shimane University Faculty of Medicine

Conflict of interest: None

[Objectives] To investigate whether active synovitis defined by musculoskeletal ultrasound (US) can influence radiographic damage in rheumatoid arthritis (RA). [Methods] Fourteen RA patients who were followed by Sugiura clinic and underwent musculoskeletal US at every visit from 2012 to 2014 were retrospectively recruited. As a result, twenty-one pairs of radiographs of hands or wrists were obtained for comparing radiographic change at the baseline and almost one year later. By presence or absence of radiographic damage, 21 pairs were divided into two groups; group A included 11 pairs in which apparent radiographic joint damage was observed, whereas group B included 10 pairs in which radiographic showed no damage (n=7) or improvement (n=3). Patients backgrounds (age, sex and disease durations), clinical parameters (DAS28 and SDAI score), laboratory data (MMP-3), treatments as well as duration of active synovitis determined by musculoskeletal US (above grade 2 by power Doppler methods) were compared between the two groups by multiple regression test. [Results] Among several parameters, only duration of active synovitis were involvement in radiographic progression (OR=1.29 95%CI=1.01-1.64). [Conclusion] Active synovitis directly determined by US was associated with bone damage.

### P1-038

#### Efficacy of ultrasonography echo in clinical rheumatology

Junichi Fujisawa<sup>1</sup>, Naoki Kondo<sup>2</sup>, Naoko Kudo<sup>2</sup>, Naoto Endo<sup>2</sup>  
<sup>1</sup>Carrier Support Center for Resident, Niigata University Medical and Dental Hospital, Niigata, Japan, <sup>2</sup>Division of Orthopedic Surgery, Department of Regenerative and Transplant Medicine, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Conflict of interest: None

[Objective] To investigate the efficacy of ultrasonography in clinical rheumatology through case report. [Case 1] A 42-year-old female who had tender and swollen joints in hand and wrist from a year ago. Bony erosion and atrophy were not existed in the X-ray. In the ultrasonography, hypertrophy and power Doppler signal of extensor tenosynovium was observed in her wrist. So we diagnosed her RA and started Methotrexate. [Case 2] A 60-year-old male who had already taken Methotrexate 8mg/week. His RA activity was getting worse and came to our hospital. His

X-ray showed erosive change in his wrist. In his ultrasonography, hypertrophy and power Doppler signal of extensor tenosynovium of his wrist was observed. So we thought that his RA activity got worse and changed his Methotrexate dose up to 10mg/week. [Case 3] An 85-year-old female who had multiple joint pain and diagnosed pseud gout in four years ago. Her X-ray showed bony erosion and joint narrowing on her left wrist. In the ultrasonography, hypertrophy and power Doppler signal of extensor tenosynovium was observed in her left wrist. Also bony erosion was found on her left 2<sup>nd</sup> metacarpal head. So she was diagnosed RA and started Methotrexate and Golimumab. [Conclusion] Ultrasonography echo in clinical rheumatology was useful.

### P1-039

#### Roles of Collagen-crosslinking enzyme, lysyl oxidase, in rheumatoid synovial fibroblasts

Tetsuya Saito<sup>1,2</sup>, Kimito Kawahata<sup>1</sup>, Hitoshi Kohsaka<sup>1,2</sup>

<sup>1</sup>Department of Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), Tokyo, Japan, <sup>2</sup>CREST, Japan Science and Technology Agency

Conflict of interest: None

**Objective:** Current drugs for rheumatoid arthritis (RA), which target immune cells, achieve insufficient remission, although further immune suppression may cause serious infections. Thus, new drugs targeting synovial fibroblasts (SF) and the combination of drugs targeting immune cells and those targeting SF will be a promising therapy. The lysyl oxidase family (LOXs), a collagen-crosslinking enzyme, has been reported to be involved in the fibroblast activation in cancer and fibrosis models. In this study, we aimed to clarify the roles of LOXs in RA-SF. **Methods:** mRNA and protein expression of LOXs were evaluated with RT-PCR and Western blotting. Knockdown of LOXs was achieved using lentiviral shRNA transduction. Invasiveness of RA-SF was assessed with Matrigel invasion assay. Mice with collagen-induced arthritis (CIA) were treated with an inhibitor of LOXs,  $\beta$ -aminopropionitrile (BAPN). **Results:** Among 5 members of LOXs, LOX, LOXL1, and LOXL2 were expressed in RA-SF. TNF- $\alpha$  and IL-1 $\beta$  down-modulated LOX and LOXL1 expression, and up-regulated LOXL2 expression. Knockdown of LOX or LOXL2 impaired the invasiveness of RA-SF. BAPN ameliorated CIA *in vivo*. **Conclusion:** Our findings revealed that LOXs are involved in the invasiveness of RA-SF and may be a therapeutic target of RA.

### P1-040

#### Mitochondrial activation inhibits cell proliferation and secretions of MMP-3 / RANKL in RA-FLS

Takeshi Ueha<sup>1,2</sup>, Yoshitada Sakai<sup>1,3</sup>, Toshihisa Maeda<sup>4</sup>, Koji Fukuda<sup>4</sup>, Shinya Hayashi<sup>4</sup>, Yoshimichi Kobayashi<sup>3</sup>, Akira Hashiramoto<sup>5</sup>, Yasushi Miura<sup>4,6</sup>, Masahiro Kurosaka<sup>1,4</sup>

<sup>1</sup>Division of Rehabilitation Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, <sup>2</sup>NeoChemir Inc., Kobe, Japan, <sup>3</sup>Division of Rehabilitation Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, <sup>4</sup>Department of Orthopaedic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan, <sup>5</sup>Clinical Immunology, Kobe University Graduate School of Health Sciences, Kobe, Japan, <sup>6</sup>Department of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Japan

Conflict of interest: None

**[Objectives]** Joint destruction of rheumatoid arthritis (RA) proceeds by hyper proliferation of synovium and secretion of MMP-3/RANKL from fibroblast-like synoviocytes (FLS). We have reported that the expressions of mitochondria-related genes in RA-FLS were decreased, thereby the resistance for apoptosis was induced in RA-FLS. To reveal the relationship between mitochondria functions and joint destruction, we investigated the effect of mitochondrial activation in RA-FLS on the cell viability, secretions of MMPs / RANKL using AICAR (mitochondria-activation drug). **[Methods]** Effects of AICAR on mitochondria functions in RA-FLS were shown as mitochondrial DNA (mtDNA) and mRNA expressions of PGC-1 $\alpha$ , NRF-1, and TFAM using real-time PCR. Effects on cell viabilities, MMP-3/RANKL secretion were assessed by WST-assay and Western blotting with and without IL-1 $\beta$  or TNF $\alpha$  stimulations. [Re-

sults] mtDNA and mRNA expressions of mitochondria-related genes in RA-FLS were significantly increased by AICAR. AICAR inhibited cell proliferation and MMP-3 / RANKL secretion in RA-FLS, which induced by IL-1 $\beta$  or TNF $\alpha$ . **[Conclusion]** AICAR contributes to the reduction of cell viabilities and secretions of MMP-3 / RANKL in RA synovial cells, suggesting an important role of mitochondria for joint destruction of RA.

### P1-041

#### Pathological changes in Rheumatoid Arthritis synovial tissues by biological agents

Ayako Kubota<sup>1</sup>, Masayuki Sekiguchi<sup>1</sup>, Takashi Nakamura<sup>1</sup>, Yoshiyasu Miyazaki<sup>1</sup>, Ryo Takamatssu<sup>1</sup>, Toyomitsu Tsuchida<sup>2</sup>, Toru Suguro<sup>3</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Toho University School of Medicine, Tokyo, Japan, <sup>2</sup>Tsuchida Clinic, <sup>3</sup>Japan Research Institute of Artificial Joint

Conflict of interest: None

**[Objectives]** We examined biologics impacts on RA synovial tissues based on pathological findings collected during surgeries for the same patient before and after biologics. **[Methods]** Synovial tissues were collected from 17 RA joints. Inflammatory change was assessed by Rooney score. We examined correlation between pathological findings in RA synovium and disease activity under biologics. Disease activity was assessed by CDAI. ETN, IFX and TCZ was used as biological drug for 10, 5 and 2 joints respectively. **[Results]** Rooney score improved from 27.4 to 12.8 showing significant difference. Significant improvement in Rooney score was observed in all items. In remission and low after biologics, Rooney score significantly decreased in items of synovial lining cells, perivascular lymphocytic infiltration, lymph follicle and lymphocytic infiltration. Significant difference in Rooney score was not observed in moderate between before and after biologics. **[Conclusion]** With decrease observed in single layer formation in synovial lining cells, angiogenesis in sub-synovial tissue, perivascular lymphocytic infiltration and lymph follicle, improvement in inflammatory change in synovium was achieved. Pathological findings in sub-synovial tissue suggested to have reflected disease activity.

### P1-042

#### Association between the 18FDG-PET imaging and the pathological findings of rheumatoid synovitis

Chisa Okura<sup>1</sup>, Yukio Yonemoto<sup>1</sup>, Koichi Okamura<sup>1</sup>, Takahito Suto<sup>1</sup>, Kimihiko Takeuchi<sup>2</sup>, Kenji Takagishi<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine, Japan, <sup>2</sup>Department of Rheumatology, Isesaki Fukushima Hospital, Japan

Conflict of interest: None

**[Objectives]** It has been reported that 18FDG-PET (PET) is useful in the evaluation of RA disease activity. However, the mechanism underlying the uptake of FDG into the inflamed joint is still unclear. The aim of this study was to investigate the associations between the amount of FDG uptake in RA joints and the inflammatory findings with regard to the pathology of the synovium. **[Methods]** We performed PET in 18 of RA patients who underwent TKA surgery in our hospital just prior to surgery. We calculated FDG uptake as SUV max and scored using the Rooney score, pathological evaluation of the RA synovial tissues. We evaluated the association among the SUV max, Rooney score, CRP and ESR just before surgery. **[Results]** A Significant correlation between SUV max and Total Rooney score was not observed ( $r = 0.056$ ,  $p = 0.814$ ), but some of the individual items in the Rooney score, including the "synoviocyte hyperplasia" and "diffuse infiltrates of lymphocytes" also showed significant correlations with the SUVmax ( $r = 0.512$ ,  $p = 0.021$  and  $r = 0.581$ ,  $p = 0.007$ , respectively). **[Conclusion]** The accumulation of FDG was associated with the extent of "synoviocyte hyperplasia" and "diffuse infiltrates of lymphocytes".

### P1-043

#### Which clinical findings affect MMP-3? How much do clinical findings affect MMP-3? The swelling of knee joints strongly affected the value of MMP-3

Koji Funahashi<sup>1,2</sup>, Toshihisa Kojima<sup>1</sup>, Nobunori Takahashi<sup>1</sup>, Shuji Asai<sup>1</sup>, Yutaka Yoshioka<sup>1</sup>, Toki Takemoto<sup>1</sup>, Kenya Terabe<sup>1</sup>, Nobuyuki Asai<sup>1</sup>, Naoki Ishiguro<sup>1</sup>

<sup>1</sup>Nagoya University Hospital, <sup>2</sup>Yokkaichi Municipal Hospital

Conflict of interest: None

[Objectives] To evaluate the influence on the value of MMP-3 from other clinical findings which are disease activity, concomitant glucocorticoids (GCs), eGFR, age, sex and swelling of large joints in the cross-sectional clinical data of the rheumatoid arthritis (RA) patients. [Methods] 108 patients (87 women; 80.6%) with RA were participated in this study. Clinical data were extracted from 345 visits of 108 participants from January, 2014 to July, 2014. We performed the multiple regression analysis by the stepwise method as an independent variable for DAS-28CRP4, eGFR, Methotrexate (MTX), biologics (Bio), GCs, age, sex, tenderness and swelling of knee joints for a dependent variable with the levels of MMP-3. [Results] The mean age and disease duration is 64.2 years old, 11.8 years respectively. The ratio of Stage III+IV and Class 3+4 of Steinbrocker classification is 41.7% and 16.7%, respectively. The mean dosage of MTX was 8.7mg/week. The mean dosage of GCs was 4.5mg/day. Significant variables included swelling of knee joints, the presence of MTX and Bio, eGFR as a result of multiple regression analysis. DAS28CRP4, presence of GCs, age, sex and disease duration were excluded from an independent variable. [Conclusion] The swelling of knee joints strongly affected the value of MMP-3.

### P1-044

#### Centrosomal protein 70kDa is down-regulated by decoy receptor 3 in specifically rheumatoid synovial fibroblasts

Koji Fukuda<sup>1,2</sup>, Yasushi Miura<sup>2,3</sup>, Toshihisa Maeda<sup>2</sup>, Shinya Hayashi<sup>2</sup>, Masahiro Kurosaka<sup>2</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Kakogawa West City Hospital, Kakogawa, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan, <sup>3</sup>Division of Orthopedic Science, Department Of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Japan

Conflict of interest: None

[Objectives] We newly reported that the microarray assay revealed decoy receptor 3 (DcR3), a secreted tumor necrosis factor receptor, regulates gene expression in rheumatoid synovial fibroblasts (RA-FLS) by binding to membrane-bound TL1A. The profiles indicated that centrosomal protein 70kDa (Cep70) was down-regulated by DcR3. CEP family is the active component of centrosome and plays a vital role in cell cycle progression. In this study, we studied Cep70 as one of the key molecules in DcR3-TL1A signalling in RA-FLS. [Methods] RA and osteoarthritis (OA)-FLS were stimulated with inflammatory cytokines or DcR3. RA-FLS were treated with DcR3 after pre-treatment with anti-TL1A Ab. Cep70 mRNA were quantified by real-time PCR. Cep70 in RA and OA synovium were evaluated with immunohistochemistry. [Results] Real-time PCR revealed Cep70 in RA-FLS was higher than that in OA-FLS. DcR3 decreased Cep70 in RA-FLS, but not in OA-FLS. Anti-TL1A Ab inhibited the down-regulation of Cep70 in RA-FLS induced by DcR3. Immunohistochemistry revealed that Cep70 protein was expressed more in superficial lining layer of RA synovium than that of OA synovium. [Conclusions] Cep70 was increased in RA-FLS and Cep70 expression in RA-FLS was decreased by DcR3 by binding to TL1A in a disease-specific fashion.

### P1-045

#### Secretion of Vascular Endothelial Growth Factor is Dramatically Down-regulated by the Antioxidant of N-acetylcysteine in Fibroblast-like Synoviocytes from Rheumatoid Arthritis

Hiroshige Sano<sup>1</sup>, Naoki Kondo<sup>1</sup>, Yasufumi Kijima<sup>1</sup>, Takahiro Netsu<sup>2</sup>, Naoko Kudo<sup>1</sup>, Junichi Fujisawa<sup>1</sup>, Naoto Endo<sup>1</sup>

<sup>1</sup>Division of Orthopedic Surgery, Department of Regenerative and Trans-

plant Medicine Niigata University, Graduate School of Medical and Dental Sciences, <sup>2</sup>Department of Rheumatology, Nagaoka Red Cross Hospital

Conflict of interest: None

[Objectives] The aim of this study was to investigate the effects of the antioxidant N-acetylcysteine (NAC) on vascular endothelial growth factor (VEGF) levels in human fibroblast-like synoviocytes (FLS) from patients with rheumatoid arthritis (RA). [Methods] RA-FLS were obtained from three RA patients who were undergoing joint replacement of the knee. Passaged RA-FLS were treated with or without NAC (1 mM) for 24 h. Expression levels of VEGFA mRNA and VEGF protein in the RA-FLS and also the VEGF protein secreted into the conditioned medium were measured. [Results] VEGF was significantly reduced in the conditioned media of RA-FLS after NAC treatment in two different culture media ( $p < 0.01$ ). NAC did not reduce the expression levels of VEGFA mRNA and VEGF protein in the RA-FLS, suggesting that NAC inhibited the secretion of VEGF by the RA-FLS. [Conclusion] NAC is a potent inhibitor of the secretion of VEGF in RA-FLS. This finding indicates that this compound is a candidate therapeutic agent for treating RA synovitis in the future.

### P1-046

#### Analysis for the gene expression profiles in rheumatoid synovial fibroblasts regulated by TNF-like ligand 1A (TL1A)

Toshihisa Maeda<sup>1</sup>, Yasushi Miura<sup>1,2</sup>, Koji Fukuda<sup>1,3</sup>, Shinya Hayashi<sup>1</sup>, Masahiro Kurosaka<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan, <sup>2</sup>Division of Orthopedic Science, Department of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Japan, <sup>3</sup>Department of Orthopaedic Surgery, Kakogawa City Hospital, Kakogawa, Hyogo, Japan

Conflict of interest: None

[Objectives] TNF-like ligand 1A (TL1A) is a member of TNF receptor superfamily and involved in the pathogenesis of autoimmune diseases by inducing apoptosis via intracellular death domain or promoting inflammation through the activation of NF $\kappa$ B by binding to its specific receptor death receptor 3 (DR3). In this study, we investigated the genes expression profiles regulated by TL1A in RA-FLS by comprehensive genetic analysis using microarrays. [Methods] RA-FLS were incubated with 1.0  $\mu$ g/ml TL1A for 12 h. Gene expressions were detected by microarray assay, and the relative gene expression profiles in TL1A-stimulated cells and controls were analyzed. [Results] The experiments revealed the expression profiles of genes in RA-FLS regulated by TL1A. The profiles showed that 501 genes were upregulated and 402 were downregulated among the genes whose expression variations of the TL1A-stimulated samples were more than twice of controls. The functions of the genes include such as cell adhesion, cell signaling, cell junction, regulation of cell proliferation, and regulation of cell activation. [Discussion] In this study, we first revealed the gene expression profiles in RA-FLS regulated by TL1A. TL1A-DR3/ decoy receptor 3 (DcR3) signaling is suggested the involvement in the pathogenesis of RA.

### P1-047

#### Analysis on treatment retention rate of biologics therapy in patients with rheumatoid arthritis

Yuji Hirano, Shinya Hirabara, Masaaki Isono

Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan

Conflict of interest: Yes

[Objectives] To investigate treatment retention rate of biologics (BIO) therapy and predictive factors of its continuation in patients with rheumatoid arthritis (RA). [Methods] 254 RA patients treated with any of biologics were included in this retrospective study. Switching from one biological agent to another was defined as continuation of BIO therapy. Treatment retention rate, predictors and so on were investigated. Results] Mean age was 57.8 yo. Mean RA duration was 11.3 years. Baseline disease activity were getting lower year by year. Treatment continuation

rates were 88.4% at 1 year, 82.1% at 3 years, 74.4% at 5 years and 70.4% at 7 years. Predictors of continuation of BIO therapy were shorter RA duration, fewer concomitant prednisolone, more concomitant MTX, lower disease activity, good renal function, fewer lung disease and glucose intolerance in univariate analysis. Concomitant MTX and glucose tolerance was detected as predictors of BIO continuation in multivariate analysis. [Conclusion] Longterm continuation rate of BIO therapy was about 60-70% in 7-8 years. Baseline characteristics of patients were important predictors. Comorbidities were one of the important influencers on treatment retention rate of BIO therapy.

### P1-048

#### Contribution of serum MMP-3 to the radiographic progression after 3 to 6 months therapy with MTX or MTX plus ADA

Kazuko Shiozawa<sup>1</sup>, Yasushi Tanaka<sup>1</sup>, Ryosuke Yoshihara<sup>1</sup>, Miki Murata<sup>1</sup>, Shigeaki Imura<sup>1</sup>, Natsuko Nakagawa<sup>1</sup>, Yasuhiro Terashima<sup>1</sup>, Hironobu Yokoyama<sup>1</sup>, Koji Tateishi<sup>1</sup>, Ken Takebe<sup>1</sup>, Takashi Yamane<sup>2</sup>, Chihiro Tanaka<sup>2</sup>, Noriaki Yo<sup>2</sup>, Ken Tsumiyama<sup>3</sup>, Shunichi Shiozawa<sup>3</sup>

<sup>1</sup>Kounan Kakogawa Hospital Rheumatic Disease Center, <sup>2</sup>Kakogawa West City Hospital, <sup>3</sup>Department of Medicine Rheumatic Diseases Unit, Kyushu University Beppu Hospital

Conflict of interest: None

We have previously shown that 65 out of 161 (40.4%) patients given low-dose MTX monotherapy for 1 yr and 3 yrs respectively showed no radiographic progression wherein a subgroup with no radiographic progression could be predicted at outset by lower serum MMP-3 less than 103.7 ng/ml. We here evaluated the contribution of serum MMP-3 measured 3 to 6 months after the initiation of MTX monotherapy or MTX plus adalimumab (ADA) to radiographic progression. Methods: Radiographic progression was evaluated using modified Sharp score with reference to DAS28/CRP or EULAR response. Results: Among 161 patients treated with MTX monotherapy, 96 patients were with serum MMP3 levels more than 103.7 ng/ml and structural remission was achieved in 25 out of 96 (26.0%) patients whose MMP3 levels originally exceeded 103.7 but then decreased -69 (-118 +/- 159) ng/ml after 3-6 mo. Among 134 patients treated with ADA plus MTX because of insufficient effect of MTX monotherapy, structural remission was achieved in 44 of 104 (42.3%) patients whose MMP3 levels originally exceeded 103.7 but then decreased -104 (-146+/-203) ng/ml after 3-6 mo. Conclusion: The patients with serum MMP3 levels over 103.7ng/ml require MMP3 be further decreased approximately -104 ng/ml to achieve structural remission.

### P1-049

#### Long term analysis of remission and recurrent rate of biologics in RA patients

Atsushi Ihata<sup>1,2</sup>, Koji Kobayashi<sup>2</sup>, Atsumu Osada<sup>2</sup>, Akiko Suda<sup>3</sup>, Shohei Nagaoka<sup>2</sup>

<sup>1</sup>Department of Rheumatology and Infectious Disease, Yokohama Minami Kyou Sai Hospital, Yokohama, Japan, <sup>2</sup>Department of Rheumatology, Yokohama Minami Kyou Sai Hospital, Yokohama, Japan, <sup>3</sup>Center for Rheumatic Diseases, Yokohama City University Medical Center, Yokohama, Japan

Conflict of interest: None

[Objectives] To examine the long term biologics-free remission rate and its predictive factors. [Methods] Retrospective observational study. 23 cases of patients who remained clinical remission (DAS28 (CRP) <2.6) for 3 months or more discontinued their biologics and were observed for 5 years. During observation period, relapse group and keeping remission group were compared. [Results] The induction age of whole group was 53.3±2.8 y.o. Disease duration was 3.7±0.8 years. Steinblocker's staging was (6/12/1/3), and function class was (2/19/1/0) respectively. 78.6% were used with MTX and dose was 8.4±0.3 mg weekly. The usage of corticosteroid was 5.3%. 13 cases of relapse were observed. The rate of remaining remission was 80.0% at 1yr, 73.9% at 2yrs and 34.8% at 5yrs. All patients of remaining remission group were received MTX (vs 61.5% of relapse group). Predictive factors were DAS28 (CRP) and MMP-3 at the point of discontinuation of biologics. Cut-off value of DAS28 (CRP) was 2.0 and MMP-3 was 190.2. [Conclusion] Predictive

factor which had already reported in several studies were valid in our long-term observational study. However, more strict remission standard was required for long-term bio-free remission. MMP-3 was also a promising predictive factor for long-term bio-free remission.

### P1-050

#### Serum Matrix Metalloproteinase-3 levels predict continuation rate in RA patients with Adalimumab therapy

Yosuke Hattori<sup>1</sup>, Atsushi Kaneko<sup>1</sup>, Daihei Kida<sup>1</sup>, Yuji Hirano<sup>2</sup>, Takayoshi Fujibayashi<sup>3</sup>, Nobunori Takahashi<sup>4</sup>, Kenya Terabe<sup>4</sup>, Hiroyasu Kanda<sup>1</sup>, Toshihisa Kojima<sup>4</sup>, Naoki Ishiguro<sup>4</sup>

<sup>1</sup>Department of Orthopaedic Surgery and Rheumatology, National Hospital Organization Nagoya Medical Center, <sup>2</sup>Department of Rheumatology, Toyohashi Municipal Hospital, <sup>3</sup>Department of Orthopaedic Surgery, Konan Kosei Hospital, <sup>4</sup>Department of Orthopaedic Surgery, Nagoya University Graduate School of Medicine

Conflict of interest: Yes

[Objectives] To investigate whether serum MMP-3 is the predictor for continuation rate in treatment for RA patients with biologics. [Methods] We analyzed 220 patients with adalimumab (ADA) therapy in multi-center study TBCR. We divided into 2 groups based on the improvement of serum level of MMP-3 and CRP: high rate of improvement (MMP-HR group) and low rate of improvement (MMP-LR group) in serum MMP-3 levels at 4 weeks, and: CRP-HR group and CRP-LR group in serum CRP levels at 4 weeks. We evaluated the continuation rate at 3 years in HR group and LR group. [Results] The rate of continuation in MMP-HR group (63%) is significantly higher than in MMP-LR group (45%). The rate of continuation in CRP-HR group (61%) is significantly higher than in CRP-LR group (47%). Moreover, the rate of continuation in MMP-HR and CRP-HR group (65%) is high. [Conclusion] We considered that high rate of improvement in serum MMP-3 at 4 weeks can be useful for predicting the rate of continuation in RA patients with ADA therapy.

### P1-051

#### Evaluation of prognosis prediction factor of rheumatoid arthritis patient to whom biologic agent is thrown A comparison among the cases in secondary non-responder, continued, and discontinued after remission –

Ichiro Yoshii

Yoshii Hospital from Medical Corporation Genyu

Conflict of interest: None

[Objectives] Ten years has passed since biologic agent (BIO) was indicated for rheumatoid arthritis (RA). However, price of BIO is still so expensive, that we need to consider effectiveness for each patient. We have investigated factors that could be predicted prognosis. [Methods] 140 cases were reviewed in this study. Patients were classified into three groups, who were the group with continued (C), discontinued after attaining clinical remission (RD), and discontinued due to secondary non-responder (NR). Cases who had been discontinued due to other reasons had been eliminated from this study. Disease activity index 28 (DAS28) and matrix metalloproteinase 3 (MMP-3) are measured every month, and median value of these factors in each group had been compared each other statistically with Mann-Whitney's U-test. [Results] NR demonstrated significant higher value than the other two groups in DAS28 for 3 months after start (<0.01) as well as MMP-3 improvement ratio also demonstrate significantly. MMP-3 improvement ratio in RD demonstrated lower value than the other two groups significantly in 3 months after start (<0.02) [Conclusion] DAS28, and MMP-3 improvement ratio at 3 months after BIO is thrown are reliable indices for prediction of clinical prognosis after in RA patient.

### P1-052

#### ADAMTS5 is a biomarker for the efficacy prediction of etanercept in rheumatoid arthritis

Kensei Tsuzaka, Masayoshi Nagata

Iruma Heart Hospital

Conflict of interest: Yes

[Objectives] In this study, we investigated whether the efficacy of etanercept (ETN) can be predicted by the baseline blood a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5) mRNA level. [Methods] Nineteen randomly selected active RA patients were treated with ETN. Peripheral blood samples were collected at baseline and ADAMTS5 mRNA was quantified using real-time PCR (Biologic-Mate®). [Results] Baseline ADAMTS5 mRNA levels ( $\times 10^4$ ) in the responder ( $0.97 \pm 0.57$  Index) was significantly ( $p < 0.05$ ) lower than that in the non-responder ( $1.42 \pm 0.46$  Index) at 20 wks' treatment with ETN. DAS28 at 20 wks was significantly ( $p < 0.05$ ) lower in the Low-ADAMTS5 ( $< 0.9$  Index) group than in the High-ADAMTS5 group. The accuracy, sensitivity, specificity, PPV, and NPV of the baseline Low-ADAMTS5 ( $< 0.9$  Index) for predicting the responder at 20 wks with ETN was 78.9%, 71.4%, 83.3%, 71.4%, and 83.3%, respectively. [Conclusion] The baseline ADAMTS5 mRNA level is a biomarker for prediction of the response to ETN in RA patients.

### P1-053

#### High values of serum soluble folate receptor beta may be a predictive marker of response to anti-TNF biologics in RA

Hideo Ohtsubo<sup>1</sup>, Taku Nagai<sup>2</sup>, Tadashi Nakamura<sup>3</sup>, Takemasa Matsuda<sup>1</sup>, Takami Matsuyama<sup>4</sup>

<sup>1</sup>Center for Rheumatic Diseases, Japanese Red Cross Society Kagoshima Hospital, Kagoshima, Japan, <sup>2</sup>Department of Immunology, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima City, Japan, <sup>3</sup>Section of Internal Medicine and Rheumatology, Kumamoto Shinto General Hospital, Japan, <sup>4</sup>Department of Immunology, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima City, Japan

Conflict of interest: None

[Objectives] Folate receptor beta (FRB) is expressed on most synovial infiltrated macrophages from rheumatoid arthritis patients (RA). The purpose of this study was to define whether serum soluble FRB is a predictive marker of response to anti-TNF biologic agents in RA. [Methods] Serum soluble FRB was measured by using F(ab')<sub>2</sub> anti-FRab antibody as captured antibody and biotinylated anti-FRB antibody as detection antibody. Recombinant soluble FRB as standard protein was produced from Sf21 cells transfected with a mixture of pBacPAK9 including the FRB gene without membrane portion and BacPAK6 viral DNA. Eleven RA were divided into high and low groups according to the mean of their serum soluble FRB values before the treatment. Serum soluble FRB values and DAS28CRP scores were measured before and 3 month after the treatment. [Results] No correlation was found between serum soluble FRB values and DAS28CRP scores. Four out of five RA in the high group were responsive to the treatment while three out of six RA in the low group were responsive to the treatment. In all responsive cases, their serum FRB values were decreased after the treatment. [Conclusion] The results suggest that high values of serum soluble FRB may be a predictive marker of response to anti-biologic agents in RA.

### P1-054

#### Discontinuation of Biologics in Forty Patients with Rheumatoid Arthritis: A Single-Center Two-Year Prospective Observational Study

Katsuya Nagatani, Takamasa Murosaki, Takeo Sato, Seiji Minota  
Division of Rheumatology and Clinical Immunology, Jichi Medical University, Tochigi, Japan

Conflict of interest: None

[Objectives] To evaluate the duration of discontinuation of biologics in patients with rheumatoid arthritis (RA) in clinical remission. [Methods] We registered 40 RA patients who maintained of clinical deep remission (DAS28-CRP $< 2.0$ ) for more than a year. If a patient recurred arthritis, the patient dropped out of this study. [Results] 16 patients (40%) were able to discontinue biologics for 2 years. 24 patients (60%) recurred arthritis during the study. The patients who were able to discontinue biologics for 2 years were treated with infliximab (n=4), etanercept (n=8), adalimumab (n=3), and tocilizumab (n=1). 3 patients who were able to

discontinue biologics without DMARDs were treated with etanercept (n=2) and tocilizumab (n=1). [Conclusion] During a 2-year period, 16 patients (40%) achieved bio-free remission. After maintaining deep remission by intensive treatment with biologics, discontinuation of biologics without disease flare is possible in some RA patients.

### P1-055

#### A patient in whom mHAQ 0 was achieved using biologics

Junji Hayashi

Joint Reconstruction & Rheumatic Center, Niizashiki Central General Hospital, Saitama, Japan

Conflict of interest: None

[Objectives] We investigated factors for achieving mHAQ 0 using biologics. [Methods] Subjects comprised 113 patients in whom administration of biologics had been initiated at least one year previously. The mean age at time of starting biological use was 60.2 years, the mean disease duration was 8.8 years and the mean DAS28-CRP was 4.5. These patients were divided into a group in which mHAQ 0 was achieved at the final follow-up observation (Group A) and a group in which it was not (Group B). We then extracted factors for which significant differences were observed between these two groups. [Results] Group A comprised 27 patients (23.9%) and Group B comprised 86 patients (76.1%). Factors for which significant differences were observed were: age at time of starting biological use ( $P = 0.0081$ ), class ( $P = 0.0001$ ), PSL usage rate ( $P = 0.0153$ ), PSL dosage ( $P = 0.0166$ ) and mHAQ ( $P < 0.0001$ ). Significant differences were also noted for DAS28-CRP ( $P = 0.0207$ ) and CRP ( $P = 0.0455$ ) 3 months after starting treatment and for biological continuation rate ( $P = 0.0137$ ) at the final follow-up observation. [Conclusion] mHAQ 0 is achieved when patients with younger age, milder dysfunction and without PSL usage at the time of starting biological treatment had early effectiveness.

### P1-056

#### Remission predictors in adalimumab treatment of ADA-naïve rheumatoid arthritis patients

Toshiaki Miyamoto

Department of Internal Medicine and Rheumatology, Seirei Hamamatsu General Hospital, Shizuoka, Japan

Conflict of interest: None

**Objective:** Remission and persistency rates seen at 104W in 124 ADA treated patients were reported at the JCR 2015 to show that remission was induced in 70% of patients at 52 weeks and continued until 104W. To construct an effective treatment policy in a clinical setting, we investigated remission predictors following ADA treatment. **Methods:** 111 analyzable patients were introduced to ADA. For the DAS28-ESR remission (R group: n=64) and non-remission (NR group: n=47) groups, response at initiation, 4, 8, and 12 weeks of treatment was investigated comparatively to extract the remission predictors. The cut-off value at 4 h was determined by ROC analysis. **Results:** At baseline, age, PSL concomitant use, Stage, Class etc., were significantly low in the R group compared to the NR group. Investigation of remission predictors and the cut-off value at 4W of ADA treatment extracted ESR, DAS28-ESR, and age. The respective cut-off values were 33, 3.38, and 57 yrs. ESR was  $\leq 33$  at 4W in 58/64 (90.6%) patients in the R group, and  $\leq 33$  in 20/47 (42.6%) in the NR group. **Conclusion:** In the analysis of remission predictors to investigate the 4h cut-off value, the findings demonstrated that ESR of  $\leq 33$  or DAS28-ESR  $\leq 3.38$  at week 4 of ADA treatment is a remission predictor after 2 years of treatment.

### P1-057

#### Anti-cyclic citrullinated protein antibodies as a predictor of response to Biologics therapy in RA patients

Hideki Takagi, Haruka Uno

Orthopedic Surgery, Nagoya Central Hospital

Conflict of interest: None



[Objectives] Some reports shows anti- cyclic citrullinated protein antibodies (anti-CCP) titer might be early predictor of the efficacy of biologics therapy in patients with RA. So, we investigated the correlation the efficacy of abatacept or anti-TNF therapy and the titer of anti-CCP. [Methods] 23 patients (14 abatacept, 9 anti-TNF) with RA were enrolled in the study. Clinical Assessment and blood withdrawal were done before and 24 weeks after each treatment. We compared disease activity assessed by DAS28 score between high anti-CCP titer group ( $\geq 100$ ) and lower titer group for each treatment. [Results] Six of the 14 patients treated with abatacept, and five of the 9 patients treated with anti-TNF were high anti-CCP titer and the European League Against Rheumatism (EULAR) responders (good response: 50% and 60%, moderate response: 50% and 40%). Otherwise, there were the 3 and 2 EULAR non-responders respectively in low titer group. [Conclusion] High titer of anti-CCP was associated with better response to either abatacept or anti-TNF, independently from disease activity.

### P1-058

#### Effect of biologic-naïve and biologic-switch in rheumatoid arthritis patients with biological disease-modifying antirheumatic drug (bDMARD)

Miho Karube, Yoshinori Komagata, Hideki Shimizu, Satoshi Hayakawa, Kazuhito Fukuoka, Shinya Kaname, Yoshihiro Arimura  
First Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Object] We investigated the difference in the therapeutic effect between biologic-naïve (naïve) and biologic-switch (switch) about three kinds of bDMARD in RA patients. [Method] We evaluated 85 RA patients treated with bDMARD between 2011 and 2014 who have high disease activity. The details are ABT 37 patients, GLM 34 patients, and CZP 14 patients. We examined retention rate of these three drugs, and efficacy of clinical remission (DAS28, SDAI) and functional remission (HAQ) in the naïve and switch on the each drugs. [Result] Each retention rate was 73% of ABT, 85% of GLM, and 71% of CZP in RA patients. The SDAI remission ( $\leq 3.3$ ) was 11%~ 20% in the each drugs, naïve and switch made a little difference. On the other hand, naïve was significantly higher in the HAQ remission ( $\leq 0.5$ ) in each drugs. [Conclusion] In bDMARD, an effect of the functional remission is high in biologic-naïve.

### P1-059

#### ccf-DNA in sera correlates with the disease activity of patients with RA treated with tocilizumab

Naonori Hashimoto<sup>1</sup>, Kohsuke Yoshida<sup>1</sup>, Teppei Hashimoto<sup>2,3</sup>, Yoshiko Kawasaki<sup>3</sup>, Nao Shibamura<sup>3,4</sup>, Hironori Tateishi<sup>3,4</sup>, Akira Hashiramoto<sup>1</sup>  
<sup>1</sup>Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, <sup>2</sup>Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, <sup>3</sup>Department of Rheumatology, Kobe Kaisei Hospital, Kobe, Japan, <sup>4</sup>Department of Orthopaedic Surgery, Kobe Kaisei Hospital, Kobe, Japan

Conflict of interest: None

[Objectives] Circulating cell-free DNA (ccf-DNA) is detected in sera of patients with rheumatoid arthritis (RA) and various cancer as well. Though ccf-DNA is known to be a useful biomarker not only to diagnose malignant tumors but also monitor or predict disease courses of cancer-carrier, its relevance with RA morbidity is not yet clear. In this study, we measured ccf-DNA in sera to evaluate the association with disease activities of patients with RA. [Methods] Serum samples were collected from patients treated with anti-human interleukin-6 receptor monoclonal antibody (tocilizumab; TCZ). After inactivating serum proteins, sera were analyzed to detect ccf-DNA by quantitative PCR. Patients' disease activities were observed by the simplified disease activity index (SDAI). [Results] Amounts of ccf-DNA in sera increased for 3 months after treatment started and decreased thereafter, whereas levels of both CRP and SDAI increased until 2 months after treatment. [Conclusion] ccf-DNA in sera may serve as a novel biomarker for RA which can predict the disease activity and therapeutic efficacy.

### P1-060

#### Investigating long-term QOL in rheumatoid arthritis patients with AIMS2— 4-year evaluation of treatment with biologics —

Mayumi Kaneko, Shigeru Honjo  
Honjo Rheumatism Clinic

Conflict of interest: None

[Objectives] Nurses at our clinic have been conducting a QOL survey with the use of AIMS2 since 2011 to investigate whether QOL has been maintained over the course of 4 years in patients with rheumatoid arthritis (RA) who reached their treatment goals with biologics. [Method] The subjects were RA patients who have been maintaining clinical remission or low disease activity through treatment with biologics at our clinic. A survey has been conducted since 2011 in this population, administering the AIMS2 questionnaire between the months of May and August each year. [Results] The AIMS2 questionnaire was administered to 194 patients in 2011, 243 patients in 2012, 237 patients in 2013, and 182 patients in 2014. When we compared mean values for each item of AIMS2 on a year-by-year basis, we found no major variation in any of the items, confirming that QOL was maintained over the 4-year period. [Conclusions] This study confirmed that QOL was also maintained long-term in patients who maintained clinical remission or low disease activity long-term through treatment with biologics. Nurses should participate in comprehensive disease management to control disease activity, to reduce symptoms and to improve patient-preferred outcomes.

### P1-061

#### Investigation of radiographic progression in early-stage RA patients achieved in sustained clinical good response

Mami Tamai<sup>1</sup>, Masataka Uetani<sup>2</sup>, Yoshikazu Nakashima<sup>1</sup>, Masataka Umeda<sup>1</sup>, Shoichi Fukui<sup>1</sup>, Ayako Nishino<sup>1</sup>, Takahisa Suzuki<sup>1</sup>, Yoshiro Horai<sup>1</sup>, Tomohiro Koga<sup>1</sup>, Shin-ya Kawashiri<sup>3</sup>, Naoki Iwamoto<sup>1</sup>, Kunihiro Ichinose<sup>1</sup>, Kazuhiko Arima<sup>3</sup>, Hideki Nakamura<sup>1</sup>, Tomoki Origuchi<sup>4</sup>, Kiyoshi Aoyagi<sup>3</sup>, Atsushi Kawakami<sup>1</sup>

<sup>1</sup>Department of Immunology and Rheumatology, Nagasaki University, Nagasaki, Japan, <sup>2</sup>Department of Radiological Sciences, Nagasaki University, Nagasaki, Japan, <sup>3</sup>Department of Public Health, Nagasaki University, Nagasaki, Japan, <sup>4</sup>Department of Health Sciences, Nagasaki University, Nagasaki, Japan

Conflict of interest: None

[Objectives] To examine whether MRI is useful to predict the development of radiographic progression in early-stage RA patients achieved sustained clinical good response. [Methods] Thirty-six early-stage RA patients recruited, received Gd-enhanced MRI of both wrists and finger joints and observed 1-year. All patients had been received DMARDs during 1 year after entry, and achieved favorable clinical response, defined by decrement of DAS28  $\geq 1.2$  at 3 months as well as achievement of DAS28 low disease activity or remission at 6 months. Synovitis, osteitis and bone erosion determined by Gd-enhanced MRI were scored by RAMRIS. Plain radiographic progression was studied by Genant-modified Sharp score (GmSS). [Results] Median age 55, duration 2.4months, %female 67%, IgM-RF positivity 78%, ACPA positivity 83%, median DAS28CRP 4.42, median GmSS 0. Eight patients showed delta GmSS over 1/year. In radiographic progression group, RAMRIS osteitis score, erosion score were higher, methotrexate (MTX) introduction was lower significantly. In statistic analysis, RAMRIS erosion score may contribute to radiographic progression. [Conclusion] Our present data indicate that MRI bone erosion appears to involve in radiographic outcome in early-stage RA patients achieved in sustained clinical good response.

### P1-062

#### The safety and efficacy of tofacitinib in rheumatoid arthritis

Ayumi Okuyama, Akiko Shibata, Ryota Sakai, Kentaro Chino, Tsuneo Kondo, Hirofumi Takei, Koichi Amano  
Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Saitama, Japan

Conflict of interest: None

[Objectives] To evaluate the safety and efficacy of tofacitinib (TOF) in RA patients [Methods] The medical records of 8 RA patients (7 female and 1 male) who started to take TOF from October 2013 and had been observed for more than 12 weeks were analyzed retrospectively. We also collected the peripheral blood of 8 patients at week 0, 4 and 12 to examine the number of NK cells (CD3-CD16+CD56+) by FACS. [Background] The mean age was 64.9±6.3, and the mean disease duration was 15.3±9.3 years. 7 cases had been treated with at least one biologic, and no patients had MTX. The average DAS28-ESR was 5.04±2.24. Baseline NK cell count was 255.03 ± 217.57/μL. [Results] One female patient discontinued TOF because of prolonged pharyngitis after 10 weeks. The others could be observed for more than 12 weeks. At week 12, DAS28-ESR improved to 4.36±1.7. However these changes were not significant. The average NK cell number at week 12 was 318.46 ± 191.15/μL without significant change from the baseline. Conclusion: Considering that the patients were older, had longer disease duration, had been treated by biologics in 7 cases, and most of them had some complications, disease activity tended to improve in 12 weeks by TOF. There was no significant change in NK cell number in our 7 patients

### P1-063

#### Clinical evaluation of Tofacitinib at the author's institution

Yukitaka Ueki<sup>1</sup>, Toshiyuki Aramaki<sup>1</sup>, Kosuke Fukuda<sup>1</sup>, Kaoru Terada<sup>1</sup>, Atsushi Kawakami<sup>2</sup>

<sup>1</sup>Center for Rheumatic Diseases, Sasebo Chuo Hospital, <sup>2</sup>Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences

Conflict of interest: Yes

[Objective] To evaluate the clinical efficacy and safety of Tofacitinib in RA patients. [Methods] Clinical efficacy and safety of Tofacitinib were evaluated on 15 RA patients responding poorly to Biologics treated in our hospital. Safety and efficacy of the treatment were assessed to 12 weeks. [Result] With regard to safety, there were 5 onsets of adverse events in 5 of the 15 patients (2cases: Herpes Zoster, 1case: Pneumonia, 1case: Bronchitis, 1 case: Gastric adenoma), however, all were not serious and the outcome was recovery. The average DAS28ESR before treatment was 3.72. It improved to 2.32 in 12 weeks. [Conclusions] Safety is comparatively high if attention is paid to infection and so on. Our study suggests that the usefulness of Tofacitinib is considered high for patients that respond poorly to Biologics.

### P1-064

#### Treatment with Tofacitinib for RA at our hospital

Hisato Ishikawa

Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan

Conflict of interest: None

[Purpose] Approved in Japan in March 2013 was Tofacitinib (TOF) is a molecular targeted therapy of small molecules, unlike biologics (Bio), is an agent that can be used as an oral medicine. This time, we report examined the efficacy and safety of TOF for RA patients. [Methods] 3 RA patients that are treatment with TOF for more than 24 weeks in our hospital and, I was examined that, effectiveness (DAS28-ESR), survival rate, and side effects [Results] As patient background, age is from 66-year-old to 75-year-old, and all cases were women they were switching patients from in all cases anti-TNF $\alpha$  formulation (GLM1•ETN2). MTX had been combined in the two cases (2mg-4mg). Response1 example good in the course of more than 24 weeks after administration as compared to the previous administration in DAS28-ESR is as effective, moderate response1 example, was no response 1 patients. All treatments also continues currently, side effects were not all cases. [Conclusion] In our hospital, although the effect of the TOF was different depending on the cases, significant side effects may not occur, and was able to continue the treatment in all cases. The future, by overlapping cases, by the long-term administration, it is considered necessary to require further consideration.

### P1-065

#### Reinduction of tofacitinib is safe and effective; a report of 3 cases

Shuji Nagano<sup>1</sup>, Ayumi Uchino<sup>1</sup>, Yusuke Kashiwado<sup>1</sup>, Hirokazu Shiraishi<sup>2</sup>, Yoshinobu Koyama<sup>3</sup>, Toshiyuki Ota<sup>3</sup>

<sup>1</sup>Department of Rheumatology, Aso Iizuka Hospital, <sup>2</sup>Department of Orthopedics, Aso Iizuka Hospital, <sup>3</sup>Center for Rheumatology, Aso Iizuka Hospital, <sup>4</sup>Department of Rheumatology, Okayama Red Cross Hospital

Conflict of interest: None

[Objectives] Tofacitinib has equivalent clinical effectiveness compared to biologic DMARDs. Due to several concerns about its long-term safety and high drug cost, we have to get a information whether it is possible to cease and reinduce the drug effectively as well as safely. [Case presentation] Case 1; 69yrs old female received tofacitinib monotherapy (5mg twice daily) for 160weeks, then stopped it. Her DAS28 score was 2.06 at the termination of clinical trial. Because of insufficient response to MTX, tofacitinib was reinduced at 16 week after cessation of drug. She reached the DAS remission within 24th week. Case2; 66yrs old female received tofacitinib concomitant with MTX for 196weeks, then stopped it. Her DAS28 score was 2.26. Due to disease flare, tofacitinib was reinduced at 12 weeks after cessation. She reached DAS remission by 4th week after reinduction. Case3; 71yrs old male received tofacitinib monotherapy for 196weeks, then stopped it. His DAS28 score was 1.84. Because of insufficient response to SSZ, tofacitinib was reinduced at 40 week after cessation. He reached DAS remission by 6th week after reinduction. [Conclusion] Reinduction of tofacitinib is safe and effective. Same adverse events, as seen in the first course of therapy, occurred in the second course of therapy.

### P1-066

#### Safety and efficacy of iguratimod for patients with active rheumatoid arthritis with an inadequate response to disease modifying anti-rheumatic drugs

Wataru Hirose<sup>1</sup>, Mitsuyo Matsumoto<sup>1</sup>, Toshiaki Ishizuka<sup>2</sup>, Toshihiro Nanki<sup>3</sup>

<sup>1</sup>The Hirose Clinic of Rheumatology, <sup>2</sup>Department of Pharmacology, National Defense Medical College, <sup>3</sup>Department of Clinical Research Medicine, Teikyo University

Conflict of interest: None

[Objectives] This retrospective study investigated efficacy of iguratimod in patients with rheumatoid arthritis (RA) with an inadequate response to disease modifying antirheumatic drugs (DMARDs). [Methods]50 cases with RA were investigated for 24w with LOCF method. DAS28ESR, SDAI and EULAR improvement criteria rate were analyzed. [Results]14 cases were discontinued IGU within 24w. DAS28ESR and SADI were significantly decreased. Remission rate at 24w by DAS-28ESR and SDAI were 28% and 18%. Good, moderate and no response rate by EULAR criteria were 24%, 20% and 56%. Compared to patients without remission, patients achieved DAS28ESR remission had significantly lower ESR and CRP, and patients achieved SDAI remission had significantly lower frequency of concomitant use of DMARDs except for MTX at baseline. Compared to no responder, good/moderate responder showed significantly higher number of swollen and tender joint counts, and higher score of DAS28ESR and SDAI. Compared to low disease activity group (LD), high disease activity group (HD) showed significantly better improvement in  $\Delta$ DAS28ESR and  $\Delta$ SDAI. [Conclusion] This study suggested that iguratimod was effective not only in RA patients with LD who achieved remission at higher rate but also in RA patients with HD with insufficient DMARDs.

### P1-067

#### Efficacy of iguratimod in rheumatoid arthritis patients without concomitant methotrexate

Yutaka Yoshioka<sup>1</sup>, Toshihisa Kojima<sup>1</sup>, Nobunori Takahashi<sup>1</sup>, Koji Funahashi<sup>1</sup>, Shuji Asai<sup>1</sup>, Toki Takemoto<sup>1</sup>, Kenya Terabe<sup>1</sup>, Nobuyuki Asai<sup>1</sup>, Atsushi Kaneko<sup>2</sup>, Hiroyasu Kanda<sup>2</sup>, Yuji Hirano<sup>3</sup>, Yasuhide Kanayama<sup>4</sup>, Naoki Ishiguro<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Nagoya University School of Medicine, Nagoya, Japan, <sup>2</sup>Department of Orthopedic Surgery, Nagoya Medi-

cal Center, Nagoya, Japan, <sup>3</sup>Department of Rheumatology, Toyohashi Municipal Hospital, Aichi, Japan, <sup>4</sup>Department of Orthopedic Surgery, Toyota Kouei Hospital, Aichi, Japan

Conflict of interest: None

[Objectives] Igaratimod (IGU) is a novel disease-modifying anti-rheumatic drug (DMARD) that has been prescribed in a routine care in Japan since 2012. There is a few studies that have examined the efficacy of IGU in RA patients without concomitant MTX in a routine care. In this study, we investigated the efficacy of IGU in RA patients without concomitant MTX. [Methods] Patients treated without MTX and taking IGU for longer than 24 weeks were included, from the Nagoya university-affiliated hospital. We retrospectively reviewed the clinical data. [Results] Fifty-eight patients were included in this study. Mean age was 70.4 years old and mean disease duration was 12.6 years. The reasons for inability to use MTX were adverse events of MTX and lung problem. Mean DAS28-ESR was 5.0±1.2 at baseline, and 4.2±1.6 at 24 weeks (p=0.006). According to the logistic regression analysis, the factor which was significantly associated with the achievement of low disease activity at 24 weeks were the DAS28-ESR at baseline and concomitant prednisolone. [Conclusion] These data provide support for the possible use of IGU in RA patients without concomitant MTX.

### P1-068

#### Efficacy of iguratimod for treating 117 rheumatoid arthritis (RA) patients

Tomohiko Yoshida<sup>1,2</sup>, Naooki Katsuyama<sup>1,2</sup>, Hiromasa Nakano<sup>1</sup>, Youhei Nozawa<sup>2,3</sup>

<sup>1</sup>Setagaya Rheumatology Clinic, <sup>2</sup>Toshin Yoshida Naika Clinic Rheumatology, <sup>3</sup>Sakuho municipal Chikuma Hospital

Conflict of interest: None

**Objectives:** Igaratimod (IGU) is the newest disease-modifying anti-rheumatic drug (DMARD) received regulatory approval in 2012. The efficacy of IGU was investigated with 117 RA patients at the authors' hospital. **Methods:** Of the 117 RA patients who had been administered IGU at the authors' hospital since September 2012, the survey covered the 74 patients with whom analysis was possible. These consisted of 69 females and 5 males. The mean age was 59.1 years, and the mean disease duration was 5.2 years. Of the 74 patients, 54 (73%) were concomitantly administered methotrexate, and the mean methotrexate dose was 10.4 mg/week. Using DAS28CRP, the efficacy was evaluated, and the maintenance rate, safety, etc., were investigated. **Results:** Alleviation according to the DAS28CRP was shown from week 4 of IGU administration. At week 12, 55% of patients showed remission or low disease activity; and at week, 24 37% showed remission, and 18% showed low or no disease activity. The maintenance rate for these effects was 77%. **Conclusions:** The development of effects with IGU was at least as favorable as with other DMARDs, and it is an excellent drug with respect to efficacy and maintenance rate. It is expected that it will constitute an effective therapeutic agent for RA in future.

### P1-069

#### A multi center clinical study on change of IgM-RF level by igratimod for 24weeks

Hiroyasu Kanda<sup>1</sup>, Atsushi Kaneko<sup>1</sup>, Daihei Kida<sup>1</sup>, Yosuke Hattori<sup>1</sup>, Yutaka Yoshioka<sup>2</sup>, Toshihisa Kojima<sup>2</sup>, Naoki Ishiguro<sup>2</sup>, Yasuhide Kanayama<sup>3</sup>, Yuji Hirano<sup>4</sup>

<sup>1</sup>Nagoya Medical Center, Nagoya, Japan, <sup>2</sup>Nagoya University, Nagoya, Japan, <sup>3</sup>Toyota Kosei Hospital, Toyota, Japan, <sup>4</sup>Toyohashi Municipal Hospital, Toyohashi, Japan

Conflict of interest: Yes

[Objectives] To reveal relationship between RF and DAS28-CRP of RA patients medicated with iguratimod. [Methods] Criteria for patients inclusion is as follows. 1, The patient whose RF is over 50 before medicated iguratimod. 2, The patient could register TBCR. 3, The patient could be follow up for 24weeks. We divided these patients into two groups whose improvement rate of RF is over 50% (group A, n=18), and

under 50% (group B, n=27). Clinical feature of these group is as follows. Group A (sex: female 16 male 2, age: 65.9, disease duration: 66.5months (range3-396), average of RF before medication: 211.5, average of DAS28-CRP: 4.27) Group B (sex: female 24 male 3, age: 66.1, disease duration: 114 months (range8-420), average of RF before medication: 293.0, average of DAS28-CRP: 4.19). We used Mann-whitney's U test to do statistical analysis of the two groups. [Results] In groupA, improvement rate of DAS28-CRP is 38%(range -23% to 65%). In groupB, is 14% (range -180% to 65%). statistical analysis revealed that group A has significant different of DAS28-CRP compaired with group B (p<0.01). [Conclusion] Improvement rate of RF might reflect of disease activitiy in the patients medicated iguratimod.

### P1-070

#### Efficacy and sagety of Igaratimod

Mitsuhiro Iwahashi, Katsuhiko Oi, Jiro Yamana, Rie Sasaki, Seizo Yamana  
Division of Rheumatology, Higashihiroshima Memorial Hospital

Conflict of interest: Yes

[Objectives] To exam the efficacy and safety of Igaratimod (IGR) therapy in patients with Rheumatoid Arthritis (RA) for 6 months. [Methods] Efficacy was evaluated by DAS28-CRP (3). Remission was defined as below 2.6 point of DAS28-CRP score. Safety was evaluated all the adverse events during 6 months. [Results] There were 32 patients with RA receiving IGR whose disease activity was moderate or high before treatment. 1 male, 31 female, average age 67.6 years, disease duration 13.1 years, tender joint counts 2.9, swollen joint counts 3.5, CRP 2.3 mg/dL, DAS28-CRP 3.77. After 6 months, the 7 remission of treatment with IGR were 7 remission, 6 low disease activity, 10 moderate disease activity, 2 high disease activity, 7 discontinued patients (3 no efficacy, 2 gastritis, 1 eruption, 1 PCP). Remission and low disease rate of IGR therapy without MTX was 42.1%, with MTX was 38.5%. In most patients, Rheumatoid factor and gamma globulin level were declined regardless efficacy. The number of lymphocyte was not decreased. [Conclusion] The efficacy of the IGR treatment with or without MTX was similar.

### P1-071

#### Efficacy of adding iguratimod therapy in rheumatoid arthritis patients who had inadequate response to biologic DMARDs

Toshiaki Miyamoto

Department of Internal Medicine and Rheumatology, Seirei Hamamatsu General Hospital, Shizuoka, Japan

Conflict of interest: None

**Objective** Igaratimod (IGU) was approved in June 2012 and recommended by guideline 2014 in the treatment of rheumatoid arthritis (RA). Although there have been efficacy of monotherapy and concomitant MTX in clinical trials, there have been no reports of concomitant biologic DMARDs (Bio). Therefore, we investigated efficacy of concomitant IGU therapy in RA patients who had inadequate response to Bio. **Methods** IGU were prescribed to 41 RA patients from August 2012 to October 2014, subjects were 11 patients adding IGU who had inadequate response to Bio. All of 11 patients had previously received adalimumab and concomitant MTX (mean13.8mg/week). Baseline characteristics were Mean age 54 years, mean duration of illness 9.8 years, mean duration of ADA treatment 1.9 years, corticosteroid use 27%(mean 2.3mg/day). The course of DAS28, SDAI, CDAI and remission rates were analyzed. **Results** Mean DAS28-ESR, DAS28-CRP, SDAI, CDAI were significantly decreased from the initiation of IGU treatment at 24 weeks (3.65→2.62, 2.90→1.73, 7.95→2.95, 7.04→2.75). Remission rates of DAS28-ESR, DAS28-CRP, SDAI, CDAI were 55%, 73%, 64%, 55% at 24 weeks. There were no side-effect after adding IGU. **Conclusion** IGU might be a new RA treatment option for aiming remission in patients who had inadequate response to Bio.

### P1-072

#### Experiences of Igaratimod (IGU) therapy in RA patients in a single institute

Eiko Nishi, Shota Sakaguchi, Yasufumi Kai, Toshihiko Hidaka, Hiroshi

Kuroda  
Institution of Rheumatology, Zenjinkai Shimin-no-Mori Hospital

Conflict of interest: None

[Objectives] To assess the efficacy and safety of Igratimod (IGU) in Rheumatoid Arthritis (RA). [Methods] Sixty-five RA patients who had been treated with IGU were evaluated. Patient background data were as follows; mean age: 65.0 years old, female rate: 87.7%, mean duration of RA: 12.5 years, Past biologics use: 12 (ETN: 5, ADA: 2, GLM: 2, TCZ: 1, CZP: 2), %MTX combination: 70.8 (%). Clinical efficacy and safety profiles (at week 0, week 12 and week 24) were assessed for patients enrolled in our institute. DAS28-ESR, SDAI and HAQ-DI was assessed and all safety data were collected. [Results] Mean DAS28-ESR (at week 0, week 12 and week 24) was 4.3/3.5 ( $p < 0.001$ )/3.4 ( $p < 0.001$ ), and mean SDAI was 15.1/10.3 ( $p < 0.01$ )/9.6 ( $p < 0.001$ ), both were significantly decreased. HAQ-DI was 0.4/0.4/0.4. Remission rate of at week 24 were as follows; DAS28-ESR: 23.3%, SDAI: 15.0%. The continuation rate of IGU at week 24 was 84.6%, and most common reasons for discontinuing is insufficient effect in 6 cases. Adverse events were observed in 4 cases (rash: 2, stomatitis: 1, stomach discomfort: 1). [Conclusion] Both DAS28-ESR and SDAI were significantly improved at 24 weeks, and HAQ-DI was maintain remission status. In the future, further examines are needed to find out about the long-term prognosis of the IGU.

### P1-073

#### Efficacy of iguratimod in RA patients with pulmonary complications

Tetsuo Takanashi, Yu Funakubo, Hideshi Yamazaki  
Center for Rheumatic Diseases, Houseikai Marunouchi Hospital, Nagano, Japan

Conflict of interest: None

[Objectives] To investigate the efficacy and safety of iguratimod (IGU) in rheumatoid arthritis (RA) patients with pulmonary complications. IGU is a small-molecule antirheumatic drug which efficacy is not inferior to that of salazosulfapyridine (SASP) in patients with active RA. Furthermore, the efficacy of the combination of additional IGU has been demonstrated when the methotrexate (MTX) monotherapy was not sufficient. In our daily clinical practice, IGU tends to be administered to cases who cannot use MTX because of their pulmonary complications. [Methods] In our department we have administered IGU to 9 cases from September 2012 to October 2014. Seven cases (5 females and 2 males) have pulmonary complications, and one of them (male) is excluded by lack of data. [Results] In most cases DAS-28 (3-ESR) and DAS-28 (3-CRP) are improved respectively. None of them discontinued by adverse event, though there were diarrhea and stomach ache. [Conclusion] Efficacy and safety of IGU in RA patients with pulmonary complications has been demonstrated.

### P1-074

#### Predictive Factors of Beneficial Response of Igratimod in patients with rheumatoid arthritis: A single center experience

Atsumu Osada<sup>1</sup>, Koji Kobayashi<sup>1</sup>, Atsushi Ihata<sup>2</sup>, Shohei Nagaoka<sup>1</sup>  
<sup>1</sup>Department of Rheumatology, Yokohama Minami Kyousai Hospital, Yokohama, Japan, <sup>2</sup>Department of Rheumatology and Infectious Disease, Yokohama Minami Kyousai Hospital, Yokohama, Japan

Conflict of interest: None

**PURPOSE:** To evaluate the efficacy of Igratimod (IGU) and the factors predicting the response to IGU in patients with rheumatoid arthritis retrospectively. **METHODS:** Thirty nine patients administrated IGU from November 2012 to September 2014 in our hospital were enrolled. DAS28-ESR, DAS28-CRP, SDAI, CDAI, mHAQ, EULAR response criteria were evaluated in thirty six patients available to observe for 24 week or more. **RESULTS:** The average age was 71.0 years old. Nine patients had renal disorder and eight patients were associated with interstitial lung disease. In 24 weeks, fourteen patients achieved low disease activity or less. Twenty patients were considered as moderate response (MR), whereas twelve as no response (NR). No statistical significance was observed between two groups in age, sex, duration of disease, and rate of

MTX or biologics medication. Serum CRP level at baseline was significantly higher in MR group. **CONCLUSIONS:** We observed effectiveness of IGU in clinical practice. It was suggested that serum CRP level at baseline may predict the response to IGU.

### P1-075

#### Efficacy of iguratimod therapy in our hospital patients with rheumatoid arthritis

Akira Furusaki, Yoshiharu Amasaki  
Department of Rheumatology, KKR Sapporo Medical Center Tonan Hospital, Sapporo, Japan

Conflict of interest: None

[Objectives] Igratimod is a new disease-modifying anti-rheumatic drug. We conducted a 24-week study on the efficacy of iguratimod in rheumatoid arthritis patients. [Methods] Twenty-two patients were enrolled in this study, started iguratimod therapy after September 2013. We evaluated patient background, SDAI and DAS28. [Results] Average age was 56.7  $\pm$  2.37 years, mean duration of disease was 8.37  $\pm$  2.00 years, sixteen of female and six of male, seventeen of patients were combined use of methotrexate, mean methotrexate dose were 11.2  $\pm$  0.89 mg/week. Five patients were administered biologics. SDAI and DAS28 at starting iguratimod therapy were 18.8  $\pm$  1.87 and 4.32  $\pm$  0.28. Eight patients were given 50 mg of iguratimod, fourteen patients were administered 25 mg of iguratimod at 24-week. SDAI and DAS28 after 24-week therapy were 12.8  $\pm$  2.08 and 3.48  $\pm$  0.31. Two patients achieved SDAI remission, and five patients achieve DAS28 remission. Low SDAI and DAS28 at starting iguratimod therapy had a tendency to clinical remissions. [Conclusion] Igratimod might be a new choice to treat rheumatoid arthritis. However, established appropriate methods of selecting patients of rheumatoid arthritis for iguratimod, might be discussed.

### P1-076

#### The efficacy of iguratimod for rheumatoid arthritis: an institution's experience

Yusuke Takeuchi, Takahiro Nunokawa, Naoto Yokogawa, Kota Shimada, Shoji Sugii  
Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center

Conflict of interest: None

[Objectives] Igratimod has been increasingly used for patients with RA at our institution. We herein addressed the utilization and efficacy of this drug. [Methods] This retrospective study comprised RA patients receiving iguratimod at Tama Metropolitan Medical Center between Dec 2012 and Aug 2014. We investigated clinical profile and disease activity by reviewing the medical records. [Results] A total of 48 patients was treated with iguratimod during the period. The mean age was 70 years. Fourteen of them were complicated with interstitial pneumonia. Of 48 patients, the disease activity at the time of initiation of the drug and three months later was available. DAS28-CRP (4) improved statistically from 3.5 to 2.8 ( $P = 0.003$ ). Eleven patients in whom iguratimod was added to methotrexate (MTX) showed statistical improvement of DAS28-ESR (4) from 4.4 to 3.6 ( $P = 0.032$ ). [Conclusion] Igratimod was often administered to elderly patients and those with ILD. This study proved the drug's efficacy, which was also shown as an additional drug to MTX.

### P1-077

#### Evaluation of RA patients who received adalimumab and achieved clinical remission

Noriko Kimura, Katsuya Suzuki, Tsutomu Takeuchi  
Division of Rheumatology, Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan

Conflict of interest: None

[Objectives] To investigate better use of adalimumab (ADA) evaluating time courses of rheumatoid arthritis (RA) patients who received ADA and achieved clinical remission. [Methods] Clinical outcomes were ret-

respectively evaluated using Disease Activity Score in 28 joints with ESR (DAS28-ESR) and clinical remission was defined as DAS28-ESR<2.6. [Results] In our institution, 122 patients underwent treatment with ADA from July 2008, and clinical remission lasted more than 6 months in 39. The mean disease duration was 4.7±7.2 years and DAS28-ESR at baseline was 4.12±0.87. Of the 39 patients, ADA was discontinued in 4 after achieving clinical remission, continued in 27, discontinued because of disease activity in 2 and discontinued because of other reasons in 6. Of the 4 patients who discontinued ADA after achieving clinical remission, 3 flared and restarted ADA. Of 27 patients who continued ADA, 22 remained clinical remission. The patients who did not remain clinical remission tended to have longer disease duration. [Conclusion] It seemed to be better to think carefully about discontinuation of ADA after achieving clinical remission. More than 80% of patients who continued ADA remained clinical remission and lasting clinical remission might be associated with shorter disease duration.

### P1-078

#### Condition factors affecting discontinuation of infliximab treatment after introducing clinical remission state

Toshihiko Hidaka<sup>1</sup>, Shota Sakaguchi<sup>1</sup>, Eiko Nishi<sup>1</sup>, Yasufumi Kai<sup>1</sup>, Hiroshi Kuroda<sup>1</sup>, Yayoi Hashiba<sup>2</sup>, Kazuyoshi Kubo<sup>2</sup>, Yasuhiro Nagatomo<sup>2</sup>, Akihiko Okayama<sup>2</sup>

<sup>1</sup>Institution of Rheumatology, Zenjinkai Shimin-no-Mori Hospital, Miyazaki, Japan, <sup>2</sup>Department of Rheumatology, Infectious Disease and Laboratory Medicine, University of Miyazaki, Internal Medicine, Miyazaki, Japan

Conflict of interest: None

[Objective] We investigated the condition factors affecting discontinuation of infliximab (IFX) in patients with the rheumatoid arthritis (RA) after introducing clinical remission. [Methods] Ninety-six patients (14 males and 82 females, mean age; 54 years) treated with IFX were examined. When patients who were administered IFX for at least 1 year sustained remission for ≥6 months and desired to discontinue IFX, IFX was discontinued. We compared the patient backgrounds between the group of sustained remission (group A) and that of non-sustained remission (B group). [Results] Thirty-two (33%) of 96 patients fulfilled a criterion of drug holidays for IFX, 18 patients (19%) discontinued IFX after due to remission. Thirteen of 18 patients (72%) sustained discontinuation of IFX without flare over 1 year. Compared with group B, both mean total treatment duration by IFX (A; 26 months vs. B; 61 months, p<0.01) and mean duration of introduction of remission (A; 8 months vs. B; 32 months, p<0.05) was significantly short, and consecutive duration of remission (A; 19 months vs. B; 10 months, p<0.05) were significantly long in group A. [Conclusion] Biologically-free remission are achievable by early introduction of remission and long duration of remission by IFX.

### P1-079

#### A study of infliximab(IFX) involving prompt dose increase to 10 mg/kg, targeting remission and administration suspension

Teruyuki Nakatani  
Kawai Hospital

Conflict of interest: None

**Methods:** The study was 10RA patients of IFX administration was initiated. Evaluation on the basis of DAS28 was carried out 14weeks after initiation of IFX administration at 3mg/kg, and the patients showing remission were then maintained at a dose of 3mg/kg, whereas the dose was increased to 10mg/kg in the case of patients showing no remission. TNF $\alpha$  and IL-6 concentrations were measured immediately before administration, and the IFX concentration before and after dose increase was measured with the dose-increase patients. **Results:** Eight patients showed remission after administration for 14weeks, and the mean DAS-28ESR was 1.90. The dose-increase patients showed remission after 22weeks, with DAS28ESR of 2.15. Comparison of the TNF $\alpha$  and IL-6 concentrations before initiation of IFX administration between the treatment groups showed that those in the dose-increase group were higher, at 1.27[pg/ml] and 86.9, respectively, than in the maintenance group, in which they were 0.77 and 12.9. In the two dose-increase patients, the IFX

concentrations were found to increase from 7.05[ $\mu$ g/ml] to 7.57, and from less than 0.10 to 6.57, as a result of the two. **Conclusions:** Remission was achieved with all patients, and the dose increase was not stepwise, but was simply prompt administration of a high dose.

### P1-080

#### Keeping remission after discontinuation of biologics by planning or by adverse events following remission more than 6 months and reinduction of remission for flared cases by DMARD in RA

Hiromitsu Takemori, Hiroshi Kanazawa

Department of Rheumatology, Aomori Prefectural Central Hospital, Aomori, Japan

Conflict of interest: None

[Objectives] To investigate keeping remission (KR) after discontinuation of biologics (Bio) by planning (PD) or by adverse events (AED) following remission more than 6 months and reinduction of remission (RR) in flared cases (F) by DMARD in RA. [Methods] 19 PD and 20 AED among 283 RA patients who were administered Bio by March 2013 were analyzed. Disease activity was defined by DAS28ESR. [Results] 1) All cases administrated, PD (KR in PD) and AED (KR in AED) on each Bio: infliximab [127, 15 (8), 8 (4)], etanercept [141, 2 (1), 9 (4)], adalimumab [32, 2 (2), 2 (1)], tocilizumab [49, 0, 1 (1)], abatacept [24, 0, 0], golimumab [13, 0, 1 (1)]. 2) Rates of KR: PD 57.9% (11/19), AED 50% (10/20). 3) Back ground of patients in KR (21) or F (18) of both PD and AED: DAS28 at start of Bio; KR 3.90±1.12, F 4.76±1.04 (p=0.023). Stage (1/2/3/4); KR 4/3/13/1, F 0/3/14/1. Disease duration; KR 4.97±5.56 y, F 7.66±5.36 y (p=0.157). 4) RR by DMARD in F: PD 87.5% (7/8), AED 60% (6/10). 5) The sum of KR and RR by DMARD after flare: PD 94.7% (18/19), AED 80% (16/20). [Conclusion] Half of AED kept remission as well as PD. KR after discontinuation of Bio was expected more in patients of moderate disease activity than high disease activity at start of Bio. Even if flared, RR was accomplished only with DMARD in the majority of cases.

### P1-081

#### Predictive marker for the remission treated with adalimumab in rheumatoid arthritis

Masaomi Yamasaki

Division of Rheumatology, Shin-Yokohama Yamasaki Clinic

Conflict of interest: None

[Objectives] To assess the clinical characteristics of rheumatoid arthritis (RA) patients treated with adalimumab (ADA) and achieved clinical remission. [Methods] Efficacy was evaluated by DAS28. [Results] 52 (6 men, 46 women, average age 52.6 years old) of RA patients were treated with ADA and enrolled in this study. Overall remission rate was 63.5% (average observation period 48.5 weeks). However there were no significant differences in the dose of MTX, duration of disease before using ADA and initial DAS28 score between RA with remission and without remission,  $\Delta$ DAS28 at 12 weeks showed significant higher in remission group (-1.7+/-0.9 vs -0.6+/-0.7, p=0.0038). [Conclusion] This study suggest that  $\Delta$ DAS28 at 12 weeks is a useful marker to detect RA with remission in ADA therapy.

### P1-082

#### Adalimumab and started methotrexate co-administered patients who achieved a bio free

Michihito Sato, Koji Nishimura, Kazutoshi Aoki

Saitama Medical Center

Conflict of interest: None

[Methods] In August 2012 receiving the results of the HOPEFUL study, co-administration initiation of adalimumab (ADA) + methotrexate (MTX) has become possible. Efficacy and safety of simultaneous administration of ADA + MTX, also I was considering the possibility of bio-free. **METHODS** In four cases that initiated ADA + MTX co-administration was evaluated the disease activity by DAS28 and SDAI before

and after 2 weeks, 6 weeks, 14 weeks, and 26 weeks. The average disease duration was 3.1 years, average DAS-CRP was 5.42, average age was 56-year-old. The patients who achieved the echo remission stopped ADA. [Results] All four cases achieved a low disease activity – remission after 2 weeks, and they achieved remission after 6 weeks. Two cases achieved echo remission canceled ADA, and they are able to maintain remission. [Conclusion] In early-onset and high disease activity patients of rheumatoid arthritis, ADA + MTX was very effective and safety.

### P1-083

#### Predictive factors for Bio-free remission in patients with RA in clinical practice

Harutsugu Okada, Kazuhiro Kurasawa, Ryutarō Yamazaki, Ayae Tanaka, Satoko Arai, Takayoshi Owada, Reika Maezawa  
Department of Pulmonary Medicine and Clinical Immunology, Dokkyo Medical University, Tochigi, Japan

Conflict of interest: None

[Objectives] To identify predictive factors for bio-free remission/low disease activity (bio-free) more than 12 months in clinical practice [Methods] 33 RA patients who received biologics more than 6 months and stopped biologics after improvement of symptoms. [Results] The subjects were 9 male and 24 female, 52.5±17.8 year at age, 3.2±4.5 years in disease duration. The used biologics were INF (n=8), ADA (7), GOL (3), ETA (12), ABT (2) and TCZ (1) and duration of biologics therapy was 23.6±12.6 months. No difference was found in remission rate at stopping biologics between those who achieved bio-free more than 12 months (group A) and those who failed (group B), but DAS28-CRP (3) at stopping biologics was higher in group A than group B (1.34±0.40; group A vs 1.74±0.80; group B). Patients whose DAS28-CRP (3) was over 2.0 at stopping biologics were in difficulty in keeping bio-free more than 12 months. No differences were found in kinds of biologics and use/dose of glucocorticoid between group A and B. Patients with MTX more than 8mg/week easily keep bio-free. Some patients with no abnormal findings in MRI imaging at stopping biologics showed flares of RA [Conclusion] Bio-free is possible in clinical practice. DAS28-CRP<2.0 and use of MTX are predictive factors for bio-free, but not MRI findings.

### P1-084

#### Discontinuation of biologics after attaining low disease activity in rheumatoid arthritis

Yoshikazu Tsuneizumi<sup>1</sup>, Hae-hyun Lee<sup>1</sup>, Tadashi Tsukeoka<sup>1</sup>, Masahiko Suzuki<sup>2</sup>

<sup>1</sup>Department of Orthopedic Surgery, Chiba Rehabilitation Center, <sup>2</sup>Center for Frontier Medical Engineering, Chiba University

Conflict of interest: None

[Objectives] The cases of discontinuation of biologic DMARD (Bio) after attaining low disease activity were examined. [Methods] 18 cases were treated with Bio in RA more than three months and were in discontinuation of Bio after attaining remission. The average age was 55.3 years old (30-76). Reasons of discontinuation and disease duration were examined. Activity of RA before and after the discontinuation of Bio was evaluated by CRP and DAS28-CRP. [Results] The following biologics were included (Inf: 10 cases, Eta: 3 cases, Toc: 3 cases, Ada: 2 cases). It was nine cases to have kept remission during follow-up after discontinuation. Bio was reused in 9 cases of flare and 8 cases were attained remission. The mean duration of remission were 11.1 (Mo) and 8.9 (Mo) of kept remission group and of flare group. The disease duration tended to be longer in flare cases. CRP and DAS28 before the discontinuation tended to be high in flare cases, but there was not the significant difference. DAS28 three months before the discontinuation and the number of DAS28 swelling joints just before the discontinuation were significantly high in flare group. [Conclusion] A half of cases kept remission after discontinuation. And deeper remission before the discontinuation was regarded as a condition.

### P1-085

#### Golimumab (GLM) for rheumatoid arthritis: The Akita Orthopedic Group on Rheumatoid Arthritis (AORA) registry

Seiya Miyamoto<sup>1</sup>, Yoichi Kataoka<sup>2</sup>, Masaaki Ogino<sup>3</sup>, Hiromi Morita<sup>4</sup>, Kunitaka Yang<sup>5</sup>, Wataru Watanabe<sup>6</sup>, Nobuhiro Ishizawa<sup>7</sup>, Kazuhiro Shoji<sup>8</sup>, Natsuo Konishi<sup>9</sup>, Hidetoshi Watanabe<sup>10</sup>, Takeshi Kashiwagura<sup>11</sup>, Masakazu Urayama<sup>12</sup>, Hiroki Ito<sup>13</sup>, Moto Kobayashi<sup>14</sup>, Tsutomu Sakuraba<sup>14</sup>, Toshiaki Aizawa<sup>15</sup>, Keiji Kamo<sup>16</sup>, Hiroshi Aonuma<sup>17</sup>, Yusuke Sugimura<sup>18</sup>, Naohisa Miyakoshi<sup>19</sup>, Yoichi Shimada<sup>19</sup>

<sup>1</sup>Department of Orthopedic Surgery, Nakadori General Hospital, Akita, Japan, <sup>2</sup>Joto Orthopedic Clinic, Akita, Japan, <sup>3</sup>Department of Orthopedic Surgery, Koto Kousei Hospital, Akita, Japan, <sup>4</sup>Morita Orthopedic Clinic, Akita, Japan, <sup>5</sup>Yang Orthopedic Clinic, Akita, Japan, <sup>6</sup>Department of Orthopedic Surgery, Honjo Daiichi Hospital, Akita, Japan, <sup>7</sup>Department of Orthopedic Surgery, Fujiwara Memorial Hospital, Akita, Japan, <sup>8</sup>Shoji Orthopedic Clinic, Akita, Japan, <sup>9</sup>Department of Orthopedic Surgery, Akita Kousei Medical Center, Akita, Japan, <sup>10</sup>Watanabe Orthopedic Clinic, Akita, Japan, <sup>11</sup>Department of Rehabilitation Medicine, Akita City Hospital, Akita, Japan, <sup>12</sup>Department of Orthopedic Surgery, Ogachi Central Hospi, Akita, Japan, <sup>13</sup>Department of Orthopedic Surgery, Yamamoto Kumiai General Hospital, Akita, Japan, <sup>14</sup>Department of Orthopedic Surgery, Hiraka General Hospital, Akita, Japan, <sup>15</sup>Department of Orthopedic Surgery, Kita Akita Municipal Hospital, Akita, Japan, <sup>16</sup>Department of Orthopedic Surgery, Akita Rosai Hospital, Akita, Japan, <sup>17</sup>Department of Orthopedic Surgery, Kakunodate Municipal Hospital, Akita, Japan, <sup>18</sup>South Akita Orthopedic Clinic, Akita, Japan, <sup>19</sup>Department of Orthopedic Surgery, Akita University Graduate School of Medicine, Akita, Japan

Conflict of interest: None

[Objectives] The objective of this study was to evaluate the efficacy of GLM in patients with rheumatoid arthritis from AORA registry. [Methods] Out of 1987 patients included in the 2014 AORA registry, 42 patients receiving GLM were enrolled in this study. The subjects were assessed using disease activity indices and persistence rates as a total group (group A) and as naive (group N) and switching (group S) subgroups. [Results] Overall, the mean age was 56 years, and 86% of subjects were female. Thirty-six patients were receiving MTX with a mean dose of 8.1 mg. DAS28-ESR improved from 4.65 to 2.33 after the 24-month treatment, with a remission rate of 69%. The mean CDAI improved from 18 to 2 after the 24-month treatment, with a remission rate of 67%. The 24-month persistence rate was 72%. Comparison between group N (20 pts) and group S (22 pts) showed that the mean age of patients was not significantly different (52 and 59 years respectively). The mean DAS28-ESR scores before and after the 24-month treatment were 4.87 and 2.08 respectively in group N, and 4.44 and 3.53 respectively in group S, indicating that the effect of treatment was greater in group N than in group S. [Conclusion] Treatment with GLM was effective in group N and group S[A1]. The efficacy was higher in group N.

### P1-086

#### Evaluation of the efficacy and safety of 7 biologics as second line treatment in RA-from data of 2129 patients with RA at University of Occupational and Environmental Health-

Naoaki Okubo, Kazuyoshi Saito, Kazuhisa Nakano, Shingo Nakayamada, Shunsuke Fukuyo, Satoshi Kubo, Ippei Miyagawa, Shintaro Hirata, Yoshiya Tanaka

The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

Conflict of interest: None

[Objective] The aim of study was to evaluate the efficacy and safety of 2nd biologics (bio) in daily clinical practice in RA. [Methods] Baseline characteristics of 1713 patients (Pts) who received bio as 2nd line treatment at our institute and their efficacy were evaluated. [Results] Pts were treated with IFX19, ETN51, ADA83, TCZ116, ABT74, GLM39 as 2nd bio. Pts with a short disease duration, high titers of ESR, CRP and MMP-3 were treated with TCZ, and ETN was chosen for elderly pts. SDAI remission (REM) after 1y treatment was achieved in pts treated with IFX39%, ADA41%, TCZ25%, ABT29%. IFX induced bio-free REM at the rate of 16% even in 2nd treatment. In contrast, the rate of achieving SDAI REM was declined in the case of 2nd line use of

GLM19% and ETN12%. In terms of switching of biologics, better outcome was observed in order of TNFi-TCZ>TNFi-TNFi>TNFi-ABT. The retention rate at 1y was ADA77%, TCZ71%, IFX68%, ETN57%, ABT58%. The rate of discontinuation due to adverse effects (AE) was low in the case of ABT. [Conclusions] IFX and ADA showed high efficacy even in the 2nd line therapy, and TCZ brought about better improvement for the pts who showed inadequate response to TNFi. However, ENT and ABT resulted in the fewer efficacies in 2nd bio, AE was hardly occurred in pts with ABT.

### P1-087

#### Successful treatment with certolizumab pegol (CZP) of refractory monoarthritis in the cases of complete remission of rheumatoid arthritis by the other biologic agents and/or DMARDs

Syuichi Koarada<sup>1</sup>, Mitsunori Komine<sup>2</sup>, Yukiko Tokuda<sup>1</sup>, Yukihide Ono<sup>1</sup>, Yuri Sadanaga<sup>1</sup>, Rie Suematsu<sup>1</sup>, Satoko Tashiro<sup>1</sup>, Nobuyuki Ono<sup>1</sup>, Akihide Ohta<sup>1</sup>, Yoshifumi Tada<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Saga University, Saga, Japan, <sup>2</sup>Tsuruta Rehabilitation Clinic

Conflict of interest: None

A pharmacological effect of biologic agent at the site of inflammation may be an important factor for the effective treatment of arthritis in rheumatoid arthritis (RA). As shown in an animal model, certolizumab pegol (CZP), PEGylated TNF inhibitor, penetrates inflamed joints more effectively than other antibodies to TNF. However, the evidence of the drug's features in human has not been reported yet and ethically the experiment in vivo was difficult. We report three cases of low disease activity/remission of RA who developed and sustained inflammatory monoarthritis of the wrist or the finger even after treatment with biologics and/or DMARDs. They were then all treated with CZP and observed in a serial color and power Doppler sonography. In all cases the positive power Doppler signal in the joint was not detected promptly. The treatment of CZP to the refractory monoarthritis of inflammatory synovitis in RA patients has not been previously described. The cases suggest that it may be associated with the feature of CZP, possible effective penetration into the site of inflammation.

### P1-088

#### Examination of MTX dose reduction on switch from anti-TNF biologics agents to Golimumab (second report)

Takashi Mitsuhashi<sup>1,2</sup>, Kenji Mannami<sup>1</sup>

<sup>1</sup>Mannami Orthopedic Clinic, <sup>2</sup>Kyoto Ohara Memorial Hospital

Conflict of interest: None

[Objectives] Higher efficacy and lower frequency of injection site reaction are generally observed in the treatment of TNF inhibitors with concomitant with MTX. In addition, allergic reaction such as skin rash tends to be observed in lack of efficacy and diminishment of those side effects and regain of efficacy are tended with increase amount of MTX. GLM is considered to differentiate from the other anti-TNF antibody regarding the purpose of concomitant with MTX because low immunogenicity among current available biologics agents. Thus, GLM monotherapy is clinically effective treatment. To prove this, decrease amount of MTX was attempted when GLM was started after TNF inhibitors. [methods] 14 RA patients with 60.9 age and 15.8 years duration by mean who had allergic reaction during TNF inhibitors treatment were enrolled into this trial. [Results] In 13 out of 14 cases GLM did not need to increase the amount of MTX after switching to GLM with decrease of MTX dose simultaneously. Furthermore, any difference in terms of efficacy based on various type of pre-treatment and safety was not observed. [Conclusion] Thus, possible consequence of dose reduction of MTX in switching to GLM after TNF inhibitor treatment under clinical practice was examined when necessary.

### P1-089

#### Early introduction of adalimumab as the first biologic agent for rheumatoid arthritis

Hiroshi Sawano

Shizuoka Rheumatism Orthopedic Rehabilitation Hospital

Conflict of interest: None

[Objectives] We introduced adalimumab (ADA) as the first biologic agent in the early stage of rheumatoid arthritis and examined the treatment results in patients who could continue the treatment for  $\geq 1$  year. [Methods] In total, 21 patients who had received ADA in combination with methotrexate (MTX) between August 2012 and October 2013 and could be followed-up for  $\geq 1$  year were examined after 52 weeks. [Results] The mean DAS28-CRP at the introduction of ADA was 4.8, which improved to 1.7 after 52 weeks, achieving a clinical remission rate of 81.0%. The improvement in the clinical remission rates was greater in the early introduction group that received ADA within <3 months after the start of MTX administration, as compared with the late administration group that received ADA at  $\geq 3$  months after the start of MTX administration. Moreover, the difference observed between the two groups at approximately 3 months continued until 1 year later. [Conclusion] A high remission rate could be achieved in the early stage by using ADA in combination with the anchor drug MTX, in order to achieve good control. As some patients have not been followed-up for 1 year, we intend to continue this study with a higher number of patients for the coming presentation.

### P1-090

#### Analysis on clinical, functional, and structural remission of intentional switching to ADA for more than 4 years after successfully stabilized the disease activity by the first Bio-therapy in 7 patients with RA

Naohiro Asada

Municipal Tsuruga Hospital, Tsuruga, Fukui, Japan

Conflict of interest: None

[Objectives] IFX or TCZ treatment was intensively changed to ADA to maintain clinical remission in patients with RA. We estimated the efficacy of treatment by ADA for more over 4 years. [Methods] The disease activity in 7 RA patients was reduced after prior treatment by IFX or TCZ, and then Bio-therapy were switched to ADA. Subsequent changes in DAS28-ESR, serum MMP3 values, HAQ scores, the doses of MTX and PSL were examined. In addition, joint deterioration or changes in bone erosion were compared by radiography. [Results] The mean DAS28-ESR at screening, after the switch, at 1 year, 2 years, 3 years and 4 years were 5.65, 2.34, 1.84, 1.87, 1.88 and 1.67, respectively. In all 7 patients, further deeper clinical remission was especially achieved from the switch to ADA at 4 years ( $p < 0.05$ ). The mean serum MMP3 values were also maintained from the switch. The mean HAQ changed from 1.68 to 0.21 at 4 years, and the patients of less than 0.5 of HAQ were 6 (85.7%). In the radiological evaluation of joints, the changes were recovery from bone erosion, joint degradation and inhibition of bone erosion in all patients. [Conclusion] Continuous treatment by ADA for 4 years resulted in high remission rates of the clinical, functional and structural assessments in 7 RA patients.

### P1-091

#### Estimation on clinical, functional, and structural remission of intentional switching to ADA after successfully stabilized the disease activity by either IFX, ETN, or TCZ treatment as the first Bio-therapy in patients with more than moderate disease activity of RA

Naohiro Asada

Municipal Tsuruga Hospital, Tsuruga, Fukui, Japan

Conflict of interest: None

[Objectives] Bio-treatment was intensively changed to ADA to maintain clinical remission in patients with RA. We estimated this trial of new Bio-switching therapy. [Methods] The disease activity in 16 RA patients was reduced after prior treatment by IFX, ETN or TCZ, and then Bio-therapy were switched to ADA. Subsequent changes in DAS28-ESR, serum MMP3 values, HAQ scores, the doses of MTX and PSL were examined. In addition, joint deterioration or changes in bone erosion were compared by radiography. [Results] The mean DAS28-ESR at screening, after the switch, at 1 year, 2 years and 3 years were 5.18, 2.29, 1.92

( $p < 0.05$ ), 1.97 and 1.91, respectively. Further deeper clinical remission was achieved from the switch to ADA. The mean serum MMP3 values were also maintained from the switch. The mean HAQ changed from 1.76 to 0.33 at the final observation period, and the patients of less than 0.5 of HAQ were 13 (81.3%). In the radiological evaluation of joints, the changes were recovery from bone erosion and joint degradation in 7 patients, and inhibition of bone erosion in 9 patients. [Conclusion] The new Bio-switching therapy to ADA resulted in high remission rates of the clinical, functional and structural assessments in RA patients.

### P1-092

#### Efficacy of switching to certolizumab pegol in RA patients with multiple swollen joint even though serological inflammation is low after treated with biologic treatment

Katsushi Ishii<sup>1</sup>, Yuichi Mochida<sup>1</sup>, Yuki Ozawa<sup>1</sup>, Risa Matsumoto<sup>1</sup>, Naoto Mitsugi<sup>2</sup>, Tomoyuki Saito<sup>3</sup>

<sup>1</sup>Center for Rheumatic Diseases, Yokohama City University Medical Center, Yokohama, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Yokohama City University Medical Center, <sup>3</sup>Department of Orthopaedic Surgery, Yokohama City University

Conflict of interest: None

[Objectives] The purpose of this study was to investigate the efficacy of switching to CZP for the cases with multiple swollen joint even though serological inflammation is low after introduced biologic treatment. [Methods] We investigated 11 RA patients with low inflammation (CRP < 1 mg/dl) and multiple swollen joints (the number of joints  $\geq 2$ ) who were treated with some biologic agents (excluded the cases treated with tocilizumab). Assessments of efficacy were performed at baseline and at week 12 using DAS28, SDAI, and the number of swollen joints. [Results] Moderate or more response of EULAR improvement criteria were observed in 70% of all cases. DAS28 and the number of swollen joints were decreased in 80%. Mean DAS28 and the number of swollen joints were decreased, but these differences did not reach statistical significances. [Conclusion] Biological agents switching to CZP was effective treatment in cases with multiple swollen joint even though serological inflammation is low after introduced biologic treatment.

### P1-093

#### Survey of the Status of Use of Biological Preparations to Treat Rheumatoid Arthritis Patients in our Institution (five report)

Yoshinori Kanai<sup>1</sup>, Ran Matsudaira<sup>1</sup>, Souichiro Nakano<sup>3</sup>, Toshio Kawamoto<sup>2</sup>, Kenjiro Yamanaka<sup>2</sup>, Yoshinari Takasaki<sup>3</sup>

<sup>1</sup>Department of Internal Medicine, Kyoundo Hospital, Tokyo, Japan, <sup>2</sup>Department of Rheumatology, Kyoundo Hospital, Tokyo, Japan, <sup>3</sup>Department of Rheumatology and Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] We conducted a survey on the status of use of six biological preparations to treat rheumatoid arthritis in our institution. [Methods] Biological preparations were used to treat 144 cases, and consisted of Infliximab (INF) in 69, Etanercept (ETN) in 66, Tocilizumab (TCZ) in 45, Adalimumab (ADA) in 15, Abatacept (ABA) in 13, Golimumab (GLM) in 22, and certolizumab (CZP) in 7 cases. [Results] Treatment was discontinued in 10 INF cases, 20 ETN, 7 TCZ, 5 ADA, 4 ABA, 2 GLM, and 2 CZP. Treatment was switched to another drug in 39 INF cases, 24 ETN, 11 TCZ, 9 ADA, 5 ABA, 4 GLM and 1 CZP. Cases in which more than one drug was used because of attenuated or inadequate efficacy or adverse events consisted of two cases in which 5 drugs were used, 7 cases in which 4 drugs were used, 9 cases in which 3 drugs were used, and 43 cases in which 2 drugs were used. The longest periods of use were: INF, 10 yr 6 mo; ETN, 9 yr 2 mo; TCZ, 7 yr 2 mo; ADA, 5 yr 11 mo; ABA, 2 yr 8 mo; GLM, 2 yr 9 mo; CZP, 11 mo. [Conclusion] Attenuation or inadequate efficacy and adverse events were observed with the biological preparations, and in the future it appears necessary to adjust the dose, dose interval, etc., of each of the drugs.

### P1-094

#### Biologics efficacy in rheumatoid arthritis after starting our new registry (ZAO registry)

Hiroharu Oki<sup>1</sup>, Suran Yang<sup>1,2</sup>, Yasushi Naganuma<sup>1</sup>, Yuya Takakubo<sup>1</sup>, Akiko Sasaki<sup>1,2</sup>, Kan Sasaki<sup>1</sup>, Hiroshi Oorui<sup>1,3</sup>, Michiaki Takagi<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Yamagata University Faculty of Medicine, Yamagata, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Tansinnkai Yoshioka Hospital, Yamagata, Japan, <sup>3</sup>Department of Orthopaedic Surgery, National Hospital Organization Yamagata National Hospital, Yamagata, Japan

Conflict of interest: None

[Object] To evaluate the effect of our new registry (ZAO registry), which started since 2012, for rheumatoid arthritis (RA) patients who treated with biologics (Bio). [Methods] We evaluated twenty-four new patients who had been diagnosed as RA and had started treatment with Bio. [Results] Mean age was 55 years, and mean duration of illness was 102 months. Eighteen patients had already treated with methotrexate at the time in first medical examination and its mean usage dose was 7.9 mg / week. Etanercept (ETN) was prescribed to 9 patients, tocilizumab (TCZ) to 5 patients, adalimumab (ADA) to 4 patients, abatacept to 3 patients, certolizumab to 2 patients, abatacept to 3 patients and infliximab to 1 patient. In 3 patients, Bio was changed because of the insufficient efficacy (ADA  $\rightarrow$  TCZ, 2 patients; ABT  $\rightarrow$  ETN, 1 patient). Mean period from first medical examination to starting treatment with Bio was 4.5 months. Mean DAS28-CRP (4) value was improve from 5.06 at base line to 3.38 at the latest follow-up after treated with Bio. On the other hand, mean HAQ-DI value only change from 0.93 to 0.72. [Conclusions] After introducing our new registry, Bio treatment quickly started against RA patients, resulted in significant improvement in DAS28-CRP but not in HAQ-DI.

### P1-095

#### An effective case of rheumatoid arthritis with golimumab treatment switching from the secondary failure of tofacitinib

Kenji Fujii

Department of Rheumatology, Fukuoka Tokushukai Medical Center

Conflict of interest: None

The patient was a 50-year-old male with 20 months duration of rheumatoid arthritis. His serological test showed positive rheumatoid factor (141IU/ml) and anti-CCP antibody (106.3U/ml) and his stage and class were 3 and 2. His treatment was started with 10 mg per week methotrexate and 7.5mg per day prednisolone from onset. However his disease activity was high, certlizumab pegol was added after 10 months from onset. Certlizumab pegol of 6 months duration was low response for his disease activities, subsequently we changed it to tofacitinib on 16th month from onset. After initiation of tofacitinib, once his DAS28-ESR, DAS-28-CRP, SDAI, CDAI decreased from 5.44 to 3.92, from 5.13 to 3.95, from 28.6 to 13.9, from 26.5 to 12.5, respectively. However his disease activities flared after 4 months from tofacitinib initiation, we switched it to 100mg monthly golimumab. After 3 month treatment of golimumab, his DAS28 achieved remission and his SDAI and CDAI reached low disease activities. Also his prednisolone was tapered. We report an effective case of rheumatoid arthritis with golimumab for secondary failure of tofacitinib.

### P1-096

#### Clinical results of Golimumab by using ultrasonography

Masahiro Tada<sup>1</sup>, Tatsuya Koike<sup>2,3</sup>, Kenji Mamoto<sup>1</sup>, Kentaro Inui<sup>1</sup>, Yuko Sugioka<sup>3</sup>, Tadashi Okano<sup>1</sup>, Hiroaki Nakamura<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Osaka City University Medical School, Osaka, Japan, <sup>2</sup>Search Institute for Bone and Arthritis Disease (SINBAD), Wakayama, Japan, <sup>3</sup>Center for Senile Degenerative Disorders (CSD), Osaka City University Medical School, Osaka, Japan

Conflict of interest: None

[Objectives] It has past three years that we are able to use Golimumab (GLM) for the patients of Rheumatoid Arthritis (RA). Good clinical results of GLM have already been reported. Whereas, there was few re-



port about evaluation by using ultrasonography (US). The aim of this study is research for clinical results of GLM by using US. [Methods] We included ten cases (female 7 and male 3 cases) by using US followed over one year. These cases have examined US at bilateral fingers and wrist (22 joints 26points). Gray scale (GS) and power doppler (PD) was scaling 4 grade and combined each. We investigated the relationship between clinical results and US findings. [Results] Average age was 63.6±11.5 years, disease duration was 12.1±8.4 years, and DAS28-ESR was 5.33±0.93 on background. Naïve and switch were 5 cases, respectively and a case used GLM 100mg. DAS28-ESR was decrease 3.40±1.08 after one year. GS was improved from 23.2±11.1 to 14.3±10.6 and PD was decrease from 10.6±4.9 to 4.7±2.9, significantly. GS of low disease activity (LDA) patients at one year was more improved than that of non LDA patient (13.6 vs 6.0, p=0.008). [Conclusion] We revealed the relationship between clinical results and US finding in RA treated GLM. Clinical efficacy of GLM was good evaluated by using US.

### P1-097

#### Influence of MTX combination on treatment outcome of certolizumab pegol in RA patients

Nobuyuki Asai<sup>1</sup>, Yasuhide Kanayama<sup>2</sup>, Toshihisa Kojima<sup>1</sup>, Nobunori Takahashi<sup>1</sup>, Koji Funahashi<sup>1</sup>, Shuji Asai<sup>1</sup>, Toki Takemoto<sup>1</sup>, Kenya Terabe<sup>1</sup>, Yutaka Yoshioka<sup>1</sup>, Naoki Ishiguro<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Nagoya University School of Medicine, Nagoya, Japan, <sup>2</sup>Department of Orthopedic Surgery, Toyota Kosei Hospital, Toyota, Japan

Conflict of interest: None

[Objectives] The present study was undertaken to investigate the influence of MTX combination on treatment outcome of certolizumab pegol (CZP) in RA patients. [Methods] This study included 53 RA patients treated with CZP whose clinical data could be followed for 24 weeks in Tsurumai Biologics Communication Registry. Continuation rates, DAS28-ESR and adverse events were compared between MTX combined group (n=42) and not combined group (n=11), and between MTX high dose group (≥10mg/w) (n=29) and low dose group (≤8mg/w) (n=13). [Results] The continuation rate for 24 weeks in combined group (66.7%) was significantly higher compared with not combined group (54.5%). The change of DAS28-ESR was 4.74 to 3.20 in combined group, and 5.11 to 4.37 in not combined group. In combined group 18.6 adverse events occurred per 100 patient-years compared with 58.0 in not combined group. The continuation rate in high dose group (76%) was significantly higher than low dose group (54%). At both baseline and 24 weeks DAS28-ESR in high dose group (4.42 to 2.84) were significantly lower than low dose group (5.49 to 3.82). [Conclusion] The treatment outcome of CZP is improved by MTX combination, and high dose MTX at starting CZP treatment brings more efficacy.

### P1-098

#### Treatment using golimumab for RA patients

Natsuko Nakagawa, Ken Takebe, Koji Tateishi, Yasuhiro Terashima, Miki Murata, Ryosuke Yoshihara, Yasushi Tanaka, Kazuko Shiozawa, Shigeaki Imura  
Kohnan Kakogawa Hospital, Rheumatic Center

Conflict of interest: None

[Objectives] Biologic agents have been changing dramatically the course of the treatment for rheumatoid arthritis (RA). We can use golimumab as the sixth biologic agents in Japan since September 2011. The purpose of this study is to evaluate the effectiveness of the treatment of RA patients with golimumab. [Methods] Thirty RA patients treated with golimumab were evaluated. They have been treated with this biologic drug more than 52 weeks at November 2014. The mean age at introduction of golimumab was 59.0 year-old, 6 men and 24 women. It was the first time using biologic agents for 17 patients, and for 13 patients golimumab has been used after other biologics had been tried. [Results] At the time of follow-up, serological markers as C reactive protein and ESR decreased, although there was the differences among the patients. No serious side effects related to this biologic agents were observed in patients received this treatment. [Conclusion] The effectiveness of golimumab

for RA patients was reported. This biologic agents' therapy is thought to be useful for RA patients. This drug will be considered as an option for RA treatment. The experiences and clinical information about this biologic drug will be needed more in future.

### P1-099

#### Predictors of Effectiveness in Golimumab Treatment in Patients with Rheumatoid Arthritis from Multicenter Registry Data

Yuji Hirano<sup>1</sup>, Masatoshi Hayashi<sup>2</sup>, Shinya Hirabara<sup>1</sup>, Nobunori Takahashi<sup>3</sup>, Yasuhide Kanayama<sup>4</sup>, Atsushi Kaneko<sup>5</sup>, Toshihisa Kojima<sup>3</sup>, Naoki Ishiguro<sup>3</sup>

<sup>1</sup>Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan, <sup>2</sup>Department of Rheumatology, Nagano Red Cross Hospital, Nagano, Japan, <sup>3</sup>Department of Orthopaedic Surgery, Nagoya Graduate School of Medicine, Nagoya, Japan, <sup>4</sup>Department of Orthopaedic Surgery and Rheumatology, Toyota, Japan, <sup>5</sup>Department of Orthopaedic Surgery and Rheumatology, Nagoya Medical Center, Nagoya, Japan

Conflict of interest: Yes

[Objectives] To investigate predictors of effectiveness in golimumab (GLM) treatment in patients with rheumatoid arthritis (RA) using multicenter registry data in Japan. [Methods] 111 RA patients treated with GLM and registered to Tsurumai Biologics Communication Registry (TBCR) were used in this study. Patients' characteristics and time course of disease activity were investigated. Good outcome group (GOgroup: DAS28-CRP<2.6 at 52w) and Not good outcome group (NGOgroup) were compared with each other with respect to baseline characteristics, baseline disease activity and disease activity at 4w. [Results] Mean age was 61.9 yo. Mean RA duration was 158.4months. MTX usage was 73.0%. Bionative was 53.2%. DAS28-CRP and SDAI at 0w-4w-12w-24w-52w were 3.99-3.24-2.92-2.81-2.72 and 20.6-14.0-11.0-10.2-9.5, respectively. There were significant differences in age, 0wMMP-3, 4wTJC, 4wESR, 4wMMP-3, 4wDAS28-CRP and 4wSDAI between GOgroup and NGOgroup. AUC of 0wMMP-3, 4wTJC and 4wDAS28-CRP were over 0.7 using ROC analysis and cut-off values were 133.3, 3 and 3.09, respectively. [Conclusion] GLM was very effective in RA patients treated with GLM over 12w. Effectiveness at 52w could be predicted using baseline characteristics and early response in GLM treatment.

### P1-100

#### Clinical significance of serum matrix metalloproteinase-3 normalization in rheumatoid arthritis patients with anti-TNF $\alpha$ therapy

Yosuke Hattori<sup>1</sup>, Atsushi Kaneko<sup>1</sup>, Daihei Kida<sup>1</sup>, Yuji Hirano<sup>2</sup>, Takayoshi Fujibayashi<sup>3</sup>, Nobunori Takahashi<sup>4</sup>, Kenya Terabe<sup>4</sup>, Hiroyasu Kanda<sup>1</sup>, Toshihisa Kojima<sup>4</sup>, Naoki Ishiguro<sup>4</sup>

<sup>1</sup>Department of Orthopaedic Surgery and Rheumatology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan, <sup>2</sup>Department of Rheumatology, Toyohashi Municipal Hospital, <sup>3</sup>Department of Orthopaedic Surgery, Konan Kosei Hospital, <sup>4</sup>Department of Orthopaedic Surgery, Nagoya University Graduate School of Medicine

Conflict of interest: Yes

[Objectives] Our aim in this study was to investigate whether serum MMP-3 is the index of remission in rheumatoid arthritis (RA) patients with anti-TNF $\alpha$  therapy. [Methods] Female RA patients (n=113) in continuation with Adalimumab therapy for 52 weeks in the multicenter study group TBCR were enrolled in this study. We divided into 3 groups: normal level of CRP (N, -) group, normal level of CRP and MMP-3 (N, N) group, and normal level of CRP and abnormal level of MMP-3 (N, ab-N) group. We evaluated the rate of DAS28-CRP remission (DAS28-CRP<2.3) at 52 weeks in 3 groups. [Results] The median DAS28-CRP at 52 weeks in (N, -) group, (N, N) group, and (N, ab-N) group was 2.2, 2.0, and 2.5, respectively. DAS28-CRP at 52 weeks in (N, N) group is significantly lower than in (N, ab-N) group. DAS28-CRP at 52 weeks in (N, -) group is lower than in (N, ab-N) group. The rate of remission at 52 weeks in (N, -) group, (N, N) group, and (N, ab-N) group was 48%, 58%, and 33%, respectively. The rate of remission at 52 weeks in (N, N) group is significantly higher than in (N, ab-N) group. [Conclusion] Normal value of serum MMP-3 and CRP can be useful for estimating the DAS28-CRP remission. We considered that serum MMP-3 can be the index of remis-

sion in RA patients with anti-TNF $\alpha$  therapy.

### P1-101

#### Clinical usefulness of adalimumab based on Bio treatment history, duration of RA, and dose of concomitant MTX ~ Remission induction and treatment continuation at 104 weeks in 124 patients ~

Toshiaki Miyamoto

Department of Internal Medicine and Rheumatology, Seirei Hamamatsu General Hospital, Shizuoka, Japan

Conflict of interest: None

**Objective** Clinical usefulness and treatment continuation following 104 weeks of ADA in RA patients were investigated. **Methods** Subjects were 124 analyzable patients introduced to ADA at the author's institution from May 2009 to October 2012. Mean age was 53 years, mean duration of illness 7.2 years. 35 patients had a duration of illness below 2 years (<2) and 89 at least 2 years ( $\geq 2$ ), 85 were Bio Naive (N), 39 were Switch (S), 96 received MTX  $\geq 10$  mg/w ( $\geq 10$ ) and 23 MTX <10 mg/w (<10). There was no significant difference in baseline disease activity. **Results** Overall DAS28 (CRP) remission rate showed clinical remission in 40% of patients from 4 weeks, 70% from 52 weeks and maintained it until 104 weeks. Changes in DAS28 (CRP) remission rates of 4, 12, 24, 52, 80, 104 weeks for the <2 and  $\geq 2$  were similar to those seen in the N and S, but differed from those in the  $\geq 10$  and < 10 mg. Overall HAQ remission rate at 104 weeks was 84%; treatment continuation rate was 73%. MTX ( $\geq 10$ ) concomitant treatment response rate was 81%. **Conclusion** Remission was induced early with ADA in about 40% of patients, 70% of patients at 52 weeks and maintained it until 104 weeks. ADA plus an adequate dose of MTX in early-stage RA and Bio Naive patients is the best approach to maximally exploit the ADA potential.

### P1-102

#### Investigation of a dose-increase method for increasing the efficacy and maintenance rate of infliximab

Tomohiko Yoshida<sup>1,2</sup>, Naooki Katsuyama<sup>1,2</sup>, Hiromasa Nakano<sup>1</sup>, Yasuhiro Otaki<sup>1,3</sup>

<sup>1</sup>Setagaya Rheumatology Clinic, <sup>2</sup>Toshin Yoshida Naika Clinic Rheumatology, <sup>3</sup>Teikyo University General Medical Education Research Center

Conflict of interest: None

**Objectives:** To investigate the efficacy of increasing the infliximab (IFX) dose to 100 or 200 mg per administration when IFX treatment of rheumatoid arthritis (RA) patients shows insufficient efficacy. **Methods:** The study was carried out with 66 patients undergoing IFX treatment (57 females (86.4%), mean age: 52.1 years, mean RA duration: 70.0 months, mean MTX dose: 11.0 mg/week, mean[w1] DAS28CRP score: 3.70). The patients were divided into 3 groups, with which the IFX dose was not increased, was increased to 100 mg, and was increased to 200 mg; and the IFX maintenance rate, and therapeutic indices such as MMP-3 and DAS28CRP were compared between the groups. **Results:** In the group with which the IFX dose was not increased after initiation, containing 27 patients, of whom 8 dropped out, the maintenance rate was 70.4%. In the group with which the IFX dose was increased to 100 mg, containing 23 patients, of whom 14 dropped out, the maintenance rate was 40.9%. In the group with which the IFX dose was increased to 200 mg, containing 16 patients, of whom one dropped out, the maintenance rate was 93.8%, and the DAS28CRP was 2.30. **Conclusions:** With patients with whom IFX showed insufficient efficacy, increasing the dose to 200 mg resulted in marked increases in maintenance rate and efficacy.

### P1-103

#### Exploration of Factors Enabling 8-Year or Longer Continuation of Etanercept (ETN) Therapy for Rheumatoid Arthritis (RA)

Toyomitsu Tsuchida<sup>1</sup>, Ayako Kubota<sup>2</sup>, Mariko Inoue<sup>3</sup>

<sup>1</sup>Tsuchida Clinic, Chiba, Japan, <sup>2</sup>Toho University, Tokyo, Japan, <sup>3</sup>The University of Tokyo, Tokyo, Japan

Conflict of interest: None

[Objectives] Long-term results of ETN, administered to patients (pts) with RA for 8 years (yr), are analyzed. [Methods] From RA pts managed at our clinic, data were extracted on pts having received ETN as the first biologic for retrospective analysis of ETN continuation rate and comparison of background variables between the ETN continuation group and the ETN discontinuation group. [Results] The study involved 248pts having begun to receive ETN treatment (ETN Tx) by Dec 2006. Their mean age was 58.1yr. Duration of illness was 9.2yr. The ETN continuation rate at 8yr (Kaplan-Meier) was 46.0%. As of Aug 2014, 98pts were continuing ETN Tx, 62 had discontinued it because of poor responses and 49 had discontinued it because of adverse events (AEs). As compared to the continuation group, disease activity at the start of ETN Tx was significantly higher in the discontinuation (due to poor responses) group (DAS28-CRP 3.93 vs 4.36, P=0.017) and age at the start of ETN was significantly higher in the discontinuation (due to AEs) group (55.7yr vs 61.5yr, P=0.003). [Conclusion] The results suggest that ETN Tx can be safely continued if started at lower age. It is additionally suggested that ETN Tx can be effectively continued in pts with lower disease activity even when the duration of illness is long.

### P1-104

#### Efficacy of certorizumab pegol with non-loading initial dose in patients with rheumatoid arthritis

Makoto Kaburaki, Shotaro Masuoka, Emiko Shindo, Mai Kawazoe, Hiroshi Sato, Kotaro Shikano, Natsuki Fujio, Sei Muraoka, Nahoko Tanaka, Kaichi Kaneko, Tatsuhiko Yamamoto, Kenji Takagi, Tomoko Hasunuma, Shinichi Kawai

Division of Rheumatology, Department of Internal Medicine School of Medicine, Faculty of Medicine, Toho of Rheumatology, Department of Internal Medicine School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan

Conflict of interest: None

[Objectives] Certorizumab pegol (CZP) has been recommended to use an initial loading dose in the drug information. We then, tried to evaluate the efficacy of CZP with non-loading case. [Methods] Clinical features of 10 rheumatoid arthritis (RA) who administrated CZP without a loading were observed at the Toho University Omori Hospital from August 2013 to August 2014. [Results] CZP was discontinued by severe skin eruption in a case. Other nine cases were categorized into maintained group for one year (Group A) and discontinued group due to inadequate response (Group B). Their clinical characteristics (Groups A and B, respectively) were as follows: average age was 51.8 (27-77) years and 56.7 (44-82) years; disease duration was 11.0 (2-24) years and 17.0 (1-39) years; Steinbrocker classification Stage I: 2vs2, Stage II: 0vs1. Stage III: 1vs0, Stage IV: 1vs3; the mean dosage of methotrexate (MTX) were 9.3mg/week vs 9.5mg/week and prednisolone (PSL) were 3.8mg/day vs 5.0mg/day; biologic drug were naive1 and switch3 vs naive 2 and switch 4; mean DAS28-CRP was 3.3 vs 4.5 at baseline; serum level of MMP-3 was 117.8 vs 304.3 at baseline. [Conclusion] We think about non-loading cases were insufficient that have high disease activity and high serum level of MMP-3 at initial administration in RA.

### P1-105

#### Examination of the predictor of the infliximab long-term continuation in the rheumatoid arthritis

Kosaku Oda

Department of Orthopedic Surgery, Takatsuki Red Cross Hospital

Conflict of interest: None

[Purpose] We examined the background factors of the long-term continuation cases of infliximab (IFX). (more than five years) [Objective] We weighed backgrounds of 24 cases that reached the cancellation, against 18 cases that continued more than five years, among 46 RA patients who had been receiving IFX in our Hospital. [Results] Mean DAS-CRP level for five years of the continuous IFX administration group was 1.81 (before administration: 4.37). The background of continuation group (vs. cancelation group) was young (52.7 vs. 60 years old, p=0.004), short disease duration (92.6 vs. 158.3 M, p=0.009), high-dose MTX before IFX start (6.3 vs. 5.41 mg/week, p=0.049), low DAS-CRP level before

IFX administration (4.44 vs. 5.17,  $p=0.047$ ). Besides, RF in the continuation group significantly showed low level from the early period, and the effect had been maintained for five years. It suggested possibility that we can predict long-term continuation, by observing RF level after the IFX introduction.

### P1-106

#### Efficacy of certolizumab pegol in patients with rheumatoid arthritis assessed by ultrasound examination

Takanori Fujimura, Takashi Fujimoto, Ryota Hara, Naoki Shimmyo, Akira Kido, Yasunori Kobata, Yasuhiro Akai, Yasuhito Tanaka  
The Center for Rheumatic Diseases, Nara Medical University, Kashihara, Japan

Conflict of interest: None

**Objectives:** Certolizumab pegol (CZP) bring rapid improvement of clinical signs and symptoms to patients with rheumatoid arthritis (RA). We assessed its efficacy in 12 weeks in RA patients by using ultrasound (US) examination. **Methods:** Eleven patients with RA were treated with CZP. The mean disease activity at baseline was 4.46 and 20.4 for disease activity score (DAS) 28 and simplified disease activity index (SDAI), respectively. At weeks 0, 2, 4 and 12 after treatment, US examination was performed at bilateral MCP, PIP, IP, and wrist joints. Gray-scale (GS) and pulse Doppler (PD) signal was recorded in each joint using semi-quantitative score (0 to 3). The sum of these scores obtained from each joint was used as GSUS and PDUS score. **Results:** At week 0, 2, 4, and 12, mean GSUS score was 21.8, 21.4, 16.8, and 15.7 respectively. Meanwhile, at week 0, 2, 4, and 12, mean PDUS score was 13.1, 10.8, 10.0, and 9.8, respectively. At week 12, both of DAS28 and SDAI were significantly lower than at baseline (3.38 vs 4.46, 20.4 vs 10.7). Three patients who achieved DAS28 remission at week 12 showed significantly lower PDUS score than patients without remission (4.3 vs 11.9,  $p=0.0305$ ). **Conclusion:** We demonstrated early-phase efficacy of CZP in RA patients by US.

### P1-107

#### Tocilizumab reduces complement C3, 4 in patients with rheumatoid arthritis

Noriaki Okumura<sup>1</sup>, Taku Kawasaki<sup>2</sup>, Kazuhiro Oda<sup>1</sup>, Shinji Imai<sup>1</sup>, Yoshitaka Matsusue<sup>1</sup>  
<sup>1</sup>Shiga University of Medical Science, Shiga, Japan, <sup>2</sup>Shiga University of Medical Science, Shiga, Japan

Conflict of interest: None

[Objectives] Reduction of complement levels have been described during anti-TNF treatment in patients with rheumatoid arthritis (RA). However, no description on changes of complement levels have been reported with Tocilizumab (TCZ). We investigated changes of complement levels during TCZ treatment compared with Infliximab (IFX) in patients with RA. [Methods] C3 and C4 concentrations were measured from 25 patients treated with TCZ and 35 patients with IFX. Major disease activity indicators were monitored before and 1 year after the initiation of treatment. [Results] Disease activities (DAS28ESR) were significantly improved in both groups (TCZ: 5.06→2.40, IFX: 4.39→3.16) after 1 year. C3 and C4 were significantly reduced after 6 months and 1 year (C3: 121.3→82.7→78.0, 120.0→104.6→102.0; C4: 24.1→13.8→11.6, 27.3→24.5→23.4), and these effects were more pronounced in the TCZ group than the IFX group significantly ( $p<0.001$ ). Especially in the TCZ group, patients showing reduction of C4 under lower limits levels had significantly lower disease activity than others. [Conclusion] TCZ reduces complement C3, 4 in patients with RA via IL-6 pathways. These results indicate C4 may be used as a biomarker for TCZ treatment for RA.

### P1-108

#### Tocilizumab therapy altered the expression ratios of master regulators of helper T cell differentiation

Yoshifumi Tada<sup>1</sup>, Syuichi Koarada<sup>1</sup>, Nobuyuki Ono<sup>1</sup>, Rie Suematsu<sup>1</sup>, Satoko Tashiro<sup>1</sup>, Yuri Sadanaga<sup>1</sup>, Yukiko Tokuda<sup>1</sup>, Yukihide Ono<sup>1</sup>, Akihide Ohta<sup>2</sup>

<sup>1</sup>Department of Rheumatology, Faculty of Medicine, Saga University,

<sup>2</sup>Department of Nursing, Faculty of Medicine, Saga University

Conflict of interest: None

[Objectives] It has been elucidated that Tocilizumab (TCZ) downregulates Th17 cell differentiation by blocking IL-6 signals. Recently, it has been shown that Treg cells were increased and Th17 cells were decreased in the peripheral blood of RA patients after TCZ therapy. We investigated the expression of transcription factors that regulate helper T cell differentiation. [Methods] RNA was extracted from peripheral blood at baseline, and after 12w and 24w of TCZ therapy, from 6 RA patients. The expression levels of Foxp3, Ror- $\gamma$ t, T-bet, and GATA3 was measured by real-time PCR. Relative expression levels were expressed as the ratios of two genes, and the changes of the ratios before and after TCZ therapy were examined. [Results] Mean DAS28ESR was 4.98, and 4 patients showed remission after TCZ therapy. The ratio of Foxp3/Ror- $\gamma$ t expression increased and that of Ror- $\gamma$ t/GATA3 expression decreased after TCZ therapy, but other ratios showed no significant tendency. No clear relationship between the changes of the expression ratios and clinical effects were observed. [Conclusion] The expression ratios of Foxp3/Ror- $\gamma$ t and Ror- $\gamma$ t/GATA3 were modulated by TCZ therapy.

### P1-109

#### Analysis of serum levels of IL-6 and CRP in RA patients with serious infections during treatment with Tocilizumab

Hirotohi Kawashima, Kentaro Takahashi, Daisuke Kashiwakuma, Itsuo Iwamoto, Shoji Yoshida, Shin-ichiro Kagami  
Research Center for Allergy and Clinical Immunology, Asahi General Hospital, Chiba, Japan

Conflict of interest: None

[Objectives] Elevated serum level of IL-6 and decreased serum level of C-reactive protein (CRP) are characteristic of administration of Tocilizumab (TCZ) to RA patients. This study aimed to analyze serum levels of IL-6 and CRP in RA patients with serious infections during treatment with TCZ. [Methods] Eight RA patients treated with TCZ were hospitalized for serious infections. Clinical characteristic and laboratory data were retrospectively assessed. [Results] Of eight patients, five patients achieved low disease activity or remission as defined DAS28-ESR  $< 3.2$  before admission. The most frequent serious infection was bacterial pneumonia in four patients, and four remaining patients were diagnosed with cellulitis, bacterial enterocolitis, peritonitis and bacterial arthritis, respectively. Serum level of IL-6 on admission was significantly elevated as compared to that before admission [median (IQR): 932.7 pg/ml (360.3-2434 pg/ml) vs 44.6 pg/ml (2.1-306.8 pg/ml)  $p = 0.003$ ]. On the other hand, serum level of CRP on admission was less than 1.0 mg/dl in seven patients [median (IQR): 0.44 mg/dl (0.02-3.76 mg/dl)]. [Conclusion] A remarkable elevation of serum IL-6 may be as a marker of serious infections during treatment with TCZ.

### P1-110

#### Effect of tocilizumab as a first-line biologic agent in patients with rheumatoid arthritis

Ken Kumagai, Yutaka Inaba, Kengo Harigane, Yoshihiro Kusayama, Taro Tezuka, Akiko Nagaoka, Tomoyuki Saito  
Department of Orthopaedic Surgery, Yokohama City University, Yokohama, Japan

Conflict of interest: None

[Objectives] We evaluated effect of tocilizumab as a first-line biologic agent in patients with rheumatoid arthritis. [Method] Twenty biologic-naive RA patients treated with tocilizumab (TCZ) were enrolled in this study. Disease Activity Score 28 CRP (DAS28-CRP) and does of methotrexate and prednisolone were assessed at baseline, 24 weeks and 48 weeks follow-up. [Results] DAS28-CRP was significantly decreased from 4.1 at baseline to 2.1 ( $P < 0.05$ ) at 24 weeks and 2.1 ( $P < 0.05$ ) at 48 weeks. Dose of methotrexate was reduced from 8.8mg to 3.8mg ( $P < 0.05$ ) at 24 weeks and 3.2mg ( $P < 0.05$ ) at 48 weeks whereas dose of prednisolone was not altered over a follow-up period. [Conclusion] This

study suggested that TCZ is effective as the first-line biologic agent for RA.

### P1-111

#### Inhibitory effects of biologic agents on serum oxidative stress –comparison of tocilizumab with TNF-inhibitors-

Arata Nakajima, Masato Sonobe, Shinji Taniguchi, Koichi Nakagawa  
Department of Orthopedics, Toho University School of Medicine, Sakura, Japan

Conflict of interest: None

[Objectives] Recent studies have pointed out relationship between rheumatoid arthritis (RA) and oxidative stress. We also showed that serum reactive oxygen metabolites (ROM) were associated with CRP and DAS28 in patients with RA. It was shown that tocilizumab (TCZ) dramatically reduced serum ROM levels, but no reports have shown comparison of TCZ with TNF-inhibitors on temporal ROM levels during treatment. [Methods] Thirty biologics-naïve RA patients were included in this study. Patients were divided into two groups; tocilizumab-group (Group T: 14 cases) and TNF-inhibitors-group (Group TN: 16 cases). Serum ROM, CRP, MMP3 levels, DAS28-ESR, CDAI, and HAQ-DI were investigated at the initiation of biologics, 12, 24 and 52 weeks. [Results] There are no significant factors except for CRP between groups at the baseline. At 12 weeks, the median ROM level was 230 U.Carr in group T and 282 U.Carr in group TN, with both in normal range. CRP was significantly low in group T ( $P<0.05$ ). At 52 weeks, the median ROM level was 270 U.Carr in group T and 376 U.Carr in group TN ( $P<0.05$ ), but no significant differences were found in other factors. [Conclusion] TCZ rapidly reduces serum oxidative stress and maintains its inhibitory effects, while TNF-inhibitors attenuate them during treatment.

### P1-112

#### Efficacy and safety of tocilizumab in patients with rheumatoid arthritis who suffered from synovitis of larger joints

Noriko Sasaki, Takayoshi Kurabayashi, Sho Sasaki, Yasushi Koyama, Shinichi Nogi, Kiri Honda, Chiho Yamada, Shinji Sato, Yasuo Suzuki  
Department of Internal Medicine Division of Rheumatology Tokai University School of Medicine

Conflict of interest: None

[Objective] To examine the efficacy and safety of tocilizumab in patients with rheumatoid arthritis (RA) who suffered from synovitis of larger joints. [Methods] We defined that RA who suffered from elbow, shoulder, knee and the hip joint as the larger joint type RA. Twenty-four RA patients who fulfilled the criteria of the larger joint type and were introduced Tocilizumab (TCZ) and TNF $\alpha$  blocker between 2008 to 2012 were evaluated efficacy and safety in 24 and 52 weeks. [Results] Of 64 patients, 16 patients were introduced TCZ and 48 patients were introduced TNF $\alpha$  blocker. Mean age and mean disease duration of patients were 54.1 years and 8.6 years. One-year persistence rate of TCZ, ETN, ADA and IFX were 100%, 87%, 63% and 87%, respectively. In TCZ group, mean percent change in DAS 28 (ESR) and DAS28 (CRP) at 24 and 52 weeks were -3.24 and -3.18 and these were the highest rate compared with those of other TNF $\alpha$  groups. The Boolean remission was also achieved in 12 patients in TCZ groups. [Conclusion] These results suggested that TCZ is more effective and safety than TNF $\alpha$  blocker for the larger joint type RA.

### P1-113

#### How to use tocilizumab and TNF blockers in treatment of patients with rheumatoid arthritis

Kiyomitsu Miyachi<sup>1</sup>, So Nomoto<sup>2</sup>

<sup>1</sup>Keigu Clinic, <sup>2</sup>Saiseikai Yokohama City Toubu Hospital

Conflict of interest: None

[Objectives] The administration of tocilizumab (TCZ) has been reported to be more effective than TNF blockers to patients with rheumatoid arthritis (RA) presenting leukocytosis or thrombocytosis. In this

study, we examine whether or not TNF blocker will be more effective than TCZ in RA patients without such presentation. [Methods] The relationship between the presence or absence of WBC: 9000 $\uparrow$  or Plt: 35 $\times$ 10<sup>4</sup> $\uparrow$  before treatment and accomplishment rates of clinical complete remission by DAS-28 CRP at Week 24 in 33 patients treated with TCZ and 74 with TNF blockers were investigated. [Results] Twelve of the 14 RA cases presenting WBC $\uparrow$  or Plt $\uparrow$  treated with TCZ achieved complete remission, however, 5 of the 20 cases treated with ETN did reach complete remission at Week 24. This difference was statistically significant with a  $X^2$  score of 6.6526 ( $P<0.01$ ). TCZ and ETN were used in 19 and 18 RA cases with patients not presenting leukocytosis and thrombocytosis, respectively. Twelve of the 18 (66.7%) cases of RA treated with ETN reached complete remission at Week 24, however, 10 of the 19 (52.6%) RA treated with TCZ reached complete remission. [Conclusion] TNF blockers may be more suitable than TCZ as a first-line therapeutic option for RA patients without thrombocytosis and leukocytosis.

### P1-114

#### Clinical efficacy of anti-TNF inhibitor and abatacept in Japanese rheumatoid arthritis patients with switching from tocilizumab

Shinya Hirabara<sup>1</sup>, Toshihisa Kojima<sup>2</sup>, Nobunori Takahashi<sup>3</sup>, Yuji Hirano<sup>1</sup>, Yuichiro Yabe<sup>3</sup>, Atsushi Kaneko<sup>4</sup>, Daihei Kida<sup>4</sup>, Hideki Takagi<sup>6</sup>, Takeshi Oguchi<sup>5</sup>, Takayoshi Fujibayashi<sup>7</sup>, Fumiaki Sugiura<sup>5</sup>, Koji Funahashi<sup>2</sup>, Masatoshi Hayashi<sup>8</sup>, Masahiro Hanabayashi<sup>9</sup>, Yosuke Hattori<sup>4</sup>, Shuji Asai<sup>2</sup>, Hiroyasu Kanda<sup>4</sup>, Tomonori Kobayakawa<sup>2</sup>, Naoki Ishiguro<sup>2</sup>

<sup>1</sup>Department of Rheumatology, Toyohashi Municipal Hospital, Aichi, Japan, <sup>2</sup>Department of Orthopedic Surgery, Nagoya University School of Medicine, Nagoya, Japan, <sup>3</sup>Department of Rheumatology, Tokyo Shinjuku Medical Center, Tokyo, Japan, <sup>4</sup>Department of Orthopedic Surgery and Rheumatology, Nagoya Medical Center, Nagoya, Japan, <sup>5</sup>Department of Orthopedic Surgery, Anjo Kosei Hospital, Aichi, Japan, <sup>6</sup>Department of Orthopedic Surgery, Nagoya Central Hospital, Aichi, Japan, <sup>7</sup>Department of Orthopedic Surgery, Konan Kosei Hospital, Aichi, Japan, <sup>8</sup>Department of Orthopedic Surgery, Nagano Red Cross Hospital, Nagano, Japan, <sup>9</sup>Department of Orthopedic Surgery, Ichinomiya Municipal Hospital, Aichi, Japan

Conflict of interest: None

[Objectives] The aim of this study was to compare the efficacy and retention rates of two classes of biologics {tumor necrosis factor inhibitors (TNFi) and abatacept (ABT)} after switching from tocilizumab (TCZ) therapy. [Methods] We performed a retrospective multicenter study of 40 patients who underwent biologic therapy for 52 weeks after switching from TCZ therapy. [Results] There was no significant difference between the two classes of drugs, except in disease durations and oral steroid use (%). Retention rates for TNFi and ABT treatment at 52 weeks were 78.6% and 80.1%, respectively. Discontinuation due to all unfavorable causes did not significantly differ among two classes of drugs in hazard ratio-based evaluations. DAS28-CRP levels were lower with TNFi compared to ABT at 24 weeks (TNFi, 3.52; ABT, 4.12,  $p=0.033$ ), but there showed no difference among these drugs at 52 weeks (TNFi, 3.55; ABT, 3.94,  $p=0.135$ ). Percentages of subsequent low disease activity of CDAI for TNFi and ABT were 46.2%, and 22.2%, respectively. [Conclusion] Our results show that patients treated with TNFi and ABT achieved significant response with no significant differences in clinical efficacy. We should consider the characteristics of each drug, and select an appropriate drug to individual cases.

### P1-115

#### Prospective study on the possibility of MTX cessation in RA patients who have remained remission with combination of MTX plus tocilizumab

Akiko Shibata, Ryota Sakai, Kentaro Chino, Tsuneo Kondo, Ayumi Okuyama, Hirofumi Takei, Koichi Amano  
Saitama Medical Center

Conflict of interest: None

[Objectives] To evaluate the possibility of MTX cessation in RA patients remained in remission with combination of MTX plus tocilizumab (TCZ). [Methods] Twenty RA patients who have been in remission with

combination of MTX plus TCZ for more than 6 months were randomly assigned to the MTX cessation group and MTX continuation group and we evaluated the efficacy of these 2 treatment strategies prospectively at week 24. [Results] Eleven were assigned to the cessation group, and Nine were to the continuation group. Patients' background characteristics at the randomization, DAS28-ESR was 1.64 and 1.16, CDAI was 4.8 and 2.6, HAQ was 0.96 and 0.71 respectively. At week 24 after randomization, DAS28-ESR was 1.79 and 1.33, CDAI was 4.9 and 2.8, but there was no significant difference between the 2 groups. The number of the patients who were in remission was eight in the cessation group and nine in the continuation group. HAQ-DI scores of the 2 groups were 0.81 and 0.70 respectively. Both groups had no progression of bone erosion in X-rays. No adverse events were seen in the cessation group. [Conclusion] The remission was almost maintained in the cessation group. MTX cessation may be possible in patients in sustained remission with TCZ plus MTX treatment, and may be safer than MTX continuation.

### P1-116

#### **Influence of 2-year tocilizumab therapy on disease activity, quality of life, prevention of joint damage and reducing of concomitant drugs in patients with rheumatoid arthritis**

Yuji Hirano, Shinya Hirabara, Masaaki Isono

Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan

Conflict of interest: None

[Objectives] Long-term outcome in tocilizumab (TCZ) therapy in RA patients is lacking. The aim of this study is to investigate influence of 2-year TCZ therapy on disease activity, quality of life, prevention of joint damage and reducing of concomitant drugs in patients with RA. [Methods] 42 cases were used for drug retention rate and 19 cases who continued 2-year TCZ therapy were used for detailed analysis. [Results] Drug retention rates of TCZ were 87.1% at 1 year, 75.4% at 2 years, 70.7% at 3 years, 70.7% at 4 years and 64.3% at 5 years. Mean age was 58.1yo (12 females and 7 males). Mean RA duration was 7.6 years. Rates of bio-naïve was 15.8%. DAS28-CRP, CDAI and mHAQ had significantly decreased both from baseline to 1-year and from 1-year to 2-year (DAS28-CRP: 5.16/2.35/1.90, CDAI: 25.3/8.7/5.8, mHAQ: 0.75/0.46/0.35). Rates (%) of concomitant MTX and PSL at baseline, 1-year and 2-year were 73.7/47.4/26.3 and 68.4/63.2/31.6, respectively.  $\Delta$ mTSS had significantly decreased from baseline (8.8) to 3.6 during 0-1 year and to 1.2 during 1-2 year, especially in joint space narrowing score. [Conclusions] Although concomitant MTX and PSL were decreased time after time, TCZ improved disease activity and QOL in RA patients not only from baseline to 1 year but also from 1 to 2 years.

### P1-117

#### **Significance of MTX combination use with tocilizumab (TCZ) for RA patients in transition of disease activity and persistency**

Ken Hasegawa<sup>1</sup>, Shunichi Imai<sup>2</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Meinan Hospital, <sup>2</sup>Rheumatoid Arthritis Center, Minami Medical Health Cooperation

Conflict of interest: None

[Objectives] To examine the significance of Combination use of MTX with TCZ for RA patients in daily clinical practice. [Methods] Changes of CDAI were evaluated by LOCF method, and drug survival rate was calculated by Kaplan-Meier estimates in 59 RA patients (MTX combination rate: 69.5%) treated by TCZ. [Results] After 1, 2, 4, 6, 8, 10, 12, 14, 18, 24, 30, 36, 42, 48 months, in the patients treated by TCZ without/with MTX, CDAI improvement rate were 33/42%, 48/50%, 51/52%, 53/57%, 45/58%, 51/62%, 57/60%, 55/62%, 57/61%, 57/66%, 58/66%, 57/66%, 58/69%, 58/66%, CDAI50 achievement rate were 17/37%, 39/54%, 67/56%, 72/68%, 78/68%, 67/78%, 78/66%, 72/71%, 78/76%, 78/78%, 78/76%, 72/80%, 78/78%, CDAI70 achievement rate were 0/12%, 11/20%, 17/24%, 17/32%, 11/44%\*, 22/37%, 22/39%, 11/39%\*, 17/46%\*, 17/61%\*, 17/61%\*, 17/61%\*, 22/66%\*, 22/61%\*, CDAI85 achievement rate were 0/2%, 0/2%, 0/7%, 0/5%, 6/7%, 6/15%, 6/17%, 6/20%, 6/15%, 6/15%, 6/15%, 6/15%, 6/27%, 11/22% (\*P<0.05), cumulative persistency rate were 89/95%, 89/95%, 83/95%, 83/95%,

83/93%, 83/93%, 83/90%, 83/90%, 83/87%, 69/84%, 52/73%, 52/73%, 52/64% (P=0.44, Logrank test) respectively. CDAI70 achievement rate of MTX combination cases were significantly higher than that of monotherapy in long term course. [Conclusions] In TCZ therapy, MTX combination could be beneficial in long term course.

### P1-118

#### **Comparison of the effect and continuation rate of tocilizumab in combination with and without concomitantly used methotrexate in the treatment of RA**

Akihiro Toujima<sup>1</sup>, Fumio Shinomiya<sup>2</sup>, Noriaki Mima<sup>2</sup>, Kenji Tani<sup>3</sup>, Shino Yuasa<sup>3</sup>

<sup>1</sup>Department of Rheumatology, JA Anan Kyousei Hospital, <sup>2</sup>Centre for Rheumatic Disease, Mima Hospital in Yoshinogawa City, Yoshinogawa, Japan, <sup>3</sup>Department of General Medicine, Tokushima University Graduate School, Tokushima, Japan

Conflict of interest: None

[Objective] The effect and continuation rates of TCZ in combination with or without MTX were compared in the treatment of RA. [Methods] In 77 RA patients who received TCZ, changes in DAS28-ESR and MMP-3 were compared between the treatment with and without concomitant MTX. [Results] 37 subjects were treated without MTX after the start of TCZ administration and 40 subjects concomitantly received MTX. The longest TCZ administration period was 66 months, and the continuation rate remained at 70% after 2 years and onward. The rate of TCZ continuation for 2 years or longer was 67.2% in the group receiving concomitant MTX and 65% in the group not receiving MTX, thus indicating no significant inter-group difference. With or without concomitant MTX, the DAS28-ESR value stayed at a low-disease-activity level soon after the TCZ administration, without showing significant differences between the two groups. Similar results were obtained for MMP-3 and RF. [Conclusion] TCZ exerted a sufficient effect even in patients for whom MTX was not usable, and its therapeutic efficacy and continuation rate were not affected by the presence or absence of concomitantly used MTX. Thus, TCZ serves as a good biologics option for patients in whom MTX-related adverse effects are anticipated.

### P1-119

#### **Predicting clinical disease activity index remission at 24 weeks in patients with early rheumatoid arthritis treated with tocilizumab and methotrexate**

Kazushige Seki<sup>1,2</sup>, Atsunori Tokushige<sup>1,2</sup>, Takashi Imagama<sup>1,2</sup>, Mamoru Kanazawa<sup>2</sup>, Kenji Kido<sup>2</sup>, Masao Kifune<sup>2</sup>, Makoto Kubo<sup>2</sup>, Hiroshi Tanaka<sup>2</sup>, Yasuhiro Tamimoto<sup>2</sup>, Takeshi Tokito<sup>2</sup>, Kimio Nibu<sup>2</sup>, Takatomo Mine<sup>2</sup>, Noriyuki Miyazaki<sup>2</sup>, Hajime Miyazato<sup>2</sup>, Kenji Yamamoto<sup>2</sup>, Manabu Yamamoto<sup>2</sup>, Toshiko Watada<sup>2</sup>, Hiroshi Nakamura<sup>2</sup>, Shinji Fukuta<sup>2</sup>, Toshihiko Taguchi<sup>2</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan, <sup>2</sup>Yamaguchi IL-6 Meeting

Conflict of interest: Yes

[Objectives] We aimed to evaluate the efficacy of tocilizumab (TCZ) and methotrexate (MTX) in patients with early rheumatoid arthritis (RA) using the clinical disease activity index (CDAI) and to determine the baseline variables associated with CDAI remission. Twenty-three patients with active RA were enrolled. [Methods] We tried to evaluate whether baseline variables were associated with CDAI remission at 24 weeks. The rate of CDAI remission at 24 weeks was 57%. We selected baseline variables, including age, gender, duration of disease, dose of glucocorticoids and MTX, previous biologics therapy, ACPA, IgM-RF, interleukin-6, MMP-3, ESR, CRP, SJC, TJC, PtGA, EGA, DAS28-ESR, CDAI, and MHAQ. [Results] The following were significantly higher in the remission group than in the non-remission group: ESR (remission group, 64.8 ± 29.8; non-remission group, 37.0 ± 15.1) and MHAQ (0.875 ± 0.813; 0.313 ± 0.438). The strongest negative association was found between CDAI and ESR ( $r = -0.6104$ ,  $P = 0.0033$ ). ROC analysis for ESR to predict CDAI remission showed that ESR ≥ 53 mm/h was associated with CDAI remission, with a sensitivity of 75% and specificity of 88.9%. [Conclusion] In patients with RA under treatment with TCZ and MTX,

ESR has a good prognostic value for predicting CDAI remission at 24 weeks.

### P1-120

#### Study of the use of tocilizumab for rheumatoid arthritis in 2014 AORA registry

Masakazu Urayama<sup>1</sup>, Seiya Miyamoto<sup>2</sup>, Yoichi Kataoka<sup>3</sup>, Masaaki Ogino<sup>4</sup>, Hiromi Morita<sup>5</sup>, Kunitaka Yang<sup>6</sup>, Wataru Watanabe<sup>7</sup>, Nobuhiro Ishizawa<sup>8</sup>, Kazuhiro Shoji<sup>9</sup>, Natsuo Konishi<sup>10</sup>, Hidetoshi Watanabe<sup>11</sup>, Takeshi Kashiwagura<sup>12</sup>, Hiroki Ito<sup>13</sup>, Moto Kobayashi<sup>14</sup>, Tsutomu Sakuraba<sup>14</sup>, Toshiaki Aizawa<sup>15</sup>, Keiji Kamo<sup>16</sup>, Hiroshi Aonuma<sup>17</sup>, Yusuke Sugimura<sup>18</sup>, Naohisa Miyakoshi<sup>19</sup>, Yoichi Shimada<sup>19</sup>

<sup>1</sup>Department of Orthopedic Surgery, Ogachi Central Hospital, Akita, Japan, <sup>2</sup>Department of Orthopedic Surgery, Nakadori General Hospital, Akita, Japan, <sup>3</sup>Joto Orthopedic Clinic, Akita, Japan, <sup>4</sup>Department of Orthopedic Surgery, Koto Kousei Hospital, Akita, Japan, <sup>5</sup>Morita Orthopedic Clinic, Akita, Japan, <sup>6</sup>Yang Orthopedic Clinic, Akita, Japan, <sup>7</sup>Department of Orthopedic Surgery, Honjo Daiichi Hospital, Akita, Japan, <sup>8</sup>Department of Orthopedic Surgery, Fujiwara Memorial Hospital, Akita, Japan, <sup>9</sup>Shoji Orthopedic Clinic, Akita, Japan, <sup>10</sup>Department of Orthopedic Surgery, Akita Kousei Medical Center, Akita, Japan, <sup>11</sup>Watanabe Orthopedic Clinic, Akita, Japan, <sup>12</sup>Department of Rehabilitation Medicine, Akita City Hospital, Akita, Japan, <sup>13</sup>Department of Orthopedic Surgery, Yamamoto Kumiai General Hospital, Akita, Japan, <sup>14</sup>Department of Orthopedic Surgery, Hiraka General Hospital, Akita, Japan, <sup>15</sup>Department of Orthopedic Surgery, Kita Akita Municipal Hospital, Akita, Japan, <sup>16</sup>Department of Orthopedic Surgery, Akita Rosai Hospital, Akita, Japan, <sup>17</sup>Department of Orthopedic Surgery, Kakunodate Municipal Hospital, Akita, Japan, <sup>18</sup>South Akita Orthopedic Clinic, Akita, Japan, <sup>19</sup>Department of Orthopedic Surgery, Akita University Graduate School of Medicine, Akita, Japan

Conflict of interest: None

[Objectives] To investigate the use of tocilizumab (TCZ) for rheumatoid arthritis (RA). [Methods] In 117 patient treated with TCZ (63% were intravenous fluid preparation, and 37% were subcutaneous injection preparation) in 2014 AORA registry, patient background, concomitant administration of methotrexate (MTX), continuation rate, matrix metalloproteinase-3 (MMP-3), and clinical disease activity index (CDAI) were compared between the naïve (N) group and switched (S) group. [Results] In group N (53 patients, 45%) and group S (64 patients, 55%), the mean age was 59 (22-80) and 57 (32-83) years, the mean duration of disease was 124 (3-413) and 144 (14-894) months, and a total of 70% and 66% of patients received concomitant administration of MTX, respectively. The mean duration of administration was 32 (2-67) and 24 (0-54) months, and the 4-year continuation rate was 90 and 82%, respectively. MMP-3 was 93.2 (24.0-527.3) and 96.4 (23.7-294.0) ng/ml, the remission rate was 26 and 25% in CDAI, and the low disease activity (LDA) rate was 82 and 70% in CDAI, respectively. [Conclusion] In both groups with the aged patients and the longer disease duration, the continuation rate and the LDA rate were high.

### P1-121

#### Investigation of patients administered biologics at this hospital

Hideo Ohtsubo<sup>1</sup>, Noriko Aoki<sup>1</sup>, Sanae Shigemizu<sup>1</sup>, Masaki Akimoto<sup>1</sup>, Tomoe Kaieda<sup>1</sup>, Kenji Nakano<sup>2</sup>, Yoshiya Arishima<sup>2</sup>, Nobuhiko Sunahara<sup>2</sup>, Takemasa Matsuda<sup>1</sup>

<sup>1</sup>Center for Rheumatic Diseases, Japanese Red Cross Society Kagoshima Hospital, Kagoshima, Japan, <sup>2</sup>Center for Rheumatic Diseases, Japanese Red Cross Society Kagoshima Hospital, Kagoshima, Japan

Conflict of interest: Yes

[Objectives] We examined the outcome and the reasons of discontinuation of biologics. [Methods] From August 2012 to September 2014 we examined RA cases twice a year. Among them 639 cases were administered biologics. We reviewed adherence, reasons of discontinuation of biologics, and complications retrospectively. [Results] Cumulative total number of patients administered biologics were 639 cases. 30% of patients were administered IFX, etanercept 20.0%, other anti-TNF agents 16.1%, TCZ 18.8%, ABT were 15.0%. Duration of RA before start of bi-

ologics were within 2years: 16.6%, 2-5 years: 20.3%, 5-10years: 23.2%. Outcome of the patients were continuation: 55.6%, discontinuation because of insufficient effects: 17.8%, because of adverse effects: 15.4%, remission: 2.3%. 114 cases were discontinued of drug administration by lack of efficacy. Among 192 IFX cases, 50 (26.0%) were stopped, TCZ 7.5%, ABT 15.2%. 38 cases were stopped because of adverse effects. Respiratory complications are 66.7% and 20.0% among IFX and TCZ patients respectively. Less TCZ patients were suffered respiratory infection. (P=0.0114) [Conclusion] We explored 639 biologics administered RA cases who visited our hospital for 2 years. Reasons for discontinuation varied according to character of each biologics.

### P1-122

#### Switches from intravenous to subcutaneous tocilizumab were effective in treatment of the rheumatoid arthritis; a case report

Tatsuya Kobayashi, Hajime Yamanaka, Hiroshi Tamai  
Shimoshizu National Hospital

Conflict of interest: None

A 70-year-old Japanese woman with rheumatoid arthritis consulted our hospital because her rheumatoid arthritis was uncontrolled with subcutaneous etanercept injection. The anti-interleukin-6 receptor antibody subcutaneous tocilizumab injection (TCZ-SC) was started at 162 mg every 2 weeks. However, treatment with TCZ-SC was also invalid. So, Intravenous tocilizumab infusion (TCZ-IV) was started at 400mg every 4 weeks. The intravenous injection was effective immediately, and the remission of all symptoms, normalization of C-reactive protein (CRP) and Matrix Metalloproteinase-3 (MMP-3) was maintained subsequently. For the period when we used subcutaneous injection, the TCZ specific IgE antibody and TCZ antibody were measured, but both were negative. Therefore, the hypothesis that subcutaneous injection did not work for for immunity abiogenesis was denied. In conclusion, it was inferred that the cause that subcutaneous injection did not work for was because blood TCZ concentrations were low. In a case of high weight and the high disease activity, in the case of invalidity, TCZ subcutaneous injection should examine the change to TCV intravenous injection.

### P1-123

#### Selection of DMARDs for the maintenance of remission or low disease activity after withdrawal of tocilizumab in RA patients: Efficacy of the tacrolimus

Hiroshi Kaneko<sup>1,2</sup>, Reo Yoshikawa<sup>2</sup>, Yoshinori Masui<sup>2</sup>, Ruka Hishinuma<sup>2</sup>, Yuko Takahashi<sup>1</sup>, Hiroyuki Yamashita<sup>1</sup>, Toshikazu Kano<sup>2</sup>, Akio Mimori<sup>1</sup>, Takeshi Umibe<sup>3</sup>, Kensei Tsuzaka<sup>4,5</sup>

<sup>1</sup>Division of Rheumatic Diseases, Department of Internal Medicine, National Center for Global Health and Medicine, Tokyo, Japan, <sup>2</sup>Department of Rheumatology, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan, <sup>3</sup>Arthritis and Lupus Center, Matsudo City Hospital, Chiba, Japan, <sup>4</sup>Department of Internal Medicine, Tokyo Dental College Ichikawa General Hospital, Chiba, Japan, <sup>5</sup>KAYTEE BIO Co., Ltd., Chiba, Japan

Conflict of interest: None

[Objectives] We discontinued tocilizumab (TCZ) for the rheumatoid arthritis (RA) patients who had clinical remission by TCZ. Furthermore, we performed an evaluation of the disease modified anti-rheumatic-drugs (DMARDs) retrospectively in case of withdrawal maintenance including clinical remission (REM) or low disease activity (LDA). [Methods] We analyzed total 43 cases that were observed until 24 weeks in three institutions. [Results] After discontinuing of TCZ, the rate of REM was 44.2% (19/43 case), the rate of LDA was a 16.3% (7/43 case), total 60.5% of cases were available for withdrawal maintenance. Withdrawal maintenance was possible in 8/18 case (44.4%) of methotrexate, 6/10 case (60.0%) of bucillamine, and 8/9 case (88.9%) of the tacrolimus (TAC). As a result of having multivariate logistic analysis, REM or LDA tended to be easy to be maintained in case of TAC (odds ratio 10). [Conclusion] TAC was effective for the maintenance of REM or LDA after discontinuing of TCZ in RA patients.

## P1-124

### Tocilizumab was available for a case of rheumatoid arthritis which developed during treatment of anti-CADM-140/MDA5 antibody-positive dermatomyositis (DM) with interstitial pneumonia

Yuka Oikawa, Okinori Murata, Nobuhito Sasaki, Ami Matsumoto, Kouko Kowata, Yukari Ninomiya, Hitoshi Kobayashi, Kohei Yamauchi  
Division of Pulmonary Medicine, Allergy, and Rheumatology, Department of Internal Medicine, Iwate Medical University, Iwate, Japan

Conflict of interest: None

The interstitial pneumonia complicated with anti-CADM-140/MDA5 antibody-positive DM has a poor prognosis. Availability of biological drugs for RA with interstitial pneumonia is not clear. A 25-year-old woman, she presented with the eruption that was typical for DM, arthralgia, a mild muscle symptom and a slight increase of the myogenic enzyme. A chest CT showed a frosted glass shadow in bilateral lower lobes. Therefore she was diagnosed Clinically amyopathic dermatomyositis (CADM) with interstitial pneumonia. Anti-CADM-140/MDA5 antibody was found positive later. Treatment was started with pulse therapy of methylprednisolone and pulse therapy of cyclophosphamide and cyclosporine (CyA) followed by oral prednisolone (PSL) 50mg/day. Her symptoms were improved. Subsequently she was treated with PSL 14mg/day and CyA 100mg/day, but she developed bilateral proximal interphalangeal joint swelling, tenderness and morning stiffness. Laboratory examination showed elevated level of anti CCP antibody. She was diagnosed RA. She was started with Tocilizumab and obtained remission without exacerbation of the interstitial pneumonia. It was suggested that we could use Tocilizumab safely for RA which was complicated with anti-CADM-140/MDA5 antibody-positive CADM with interstitial pneumonia.

## P1-125

### Lung accelerated nodulosis in a patient with rheumatoid arthritis treated with Tocilizumab

Takao Kubota

Japan Ground Self Defense Force Central Hospital

Conflict of interest: None

[Objectives] Multiple nodulosis in lung is very rarely seen in patients with rheumatoid arthritis. [Case] A 64-year-old male was referred to our department because of an abnormal shadow on chest X-ray. He had been suffering from rheumatoid arthritis for 9 years. He had been treated with tumor necrosis factor antagonist (infliximab and etanercept) for the past 7 years and 6 months. FDG/PET of the chest revealed multiple accelerated nodulosis with the longest diameter of 4.3 cm in the right lower lobe. He underwent VATS: Patho-Histological examination revealed no malignancy, or metastatic cancer. The diagnosis of lung rheumatoid nodulosis was made. Then he had been treated successfully with TCZ. He is free from lung disease with a follow-up period of 6 months. [Conclusion] This paper describes a patient with rheumatoid arthritis who developed pulmonary nodules that showed increased uptake on PET/CT scan, reviews the use of PET scanning in the diagnosis and management of rheumatoid arthritis, and successfully treated with TCZ.

## P1-126

### Clinical characteristics of rheumatoid arthritis patients with persistent remission after tocilizumab discontinuation

Kazutoshi Yukawa, Kensuke Irino, Asako Oguma, Takuya Sawabe  
Hiroshima Red Cross Hospital and Atomic-Bomb Survivors Hospital, Hiroshima, Japan

Conflict of interest: None

[Objectives] To clarify the clinical features of rheumatoid arthritis (RA) patients who had achieved remission with tocilizumab (TCZ) and maintained it over 52 weeks after TCZ discontinuation. [Methods] Remission was defined as DAS28-ESR < 2.6. Among 89 RA patients treated with TCZ since July 2008 to June 2014, three female patients met the above criteria. We statistically analyzed these patients. [Results] At the start of TCZ, age was 43±16.2 (mean±SD) years old, body weight was 46.3±5.3 kg, and disease duration was 53.0±23.5 weeks. Stage was

1.3±0.5 and all patients were class I. Tender and swollen joint counts were 2.3±0.5 and 4.0±2.2, respectively. CRP was 3.1±3.7 mg/dl, ESR was 37.7±18.0 mm/hr, RF was 66.4±83.0 IU/ml, and MMP-3 was 398.2±505.6 ng/ml. MTX dosage was 1.3±1.9 mg/week. All patients had not received biologic DMARDs. The period to achieve remission took 8.7±0.7 weeks and the remission period before TCZ discontinuation was 58.3±31.3 weeks. At TCZ discontinuation, all patients received 8mg/week of MTX. [Conclusion] The clinical characteristics for TCZ-free remission are implied as follows: 1) earlier TCZ institution, 2) shorter disease duration, 3) earlier achievement of remission with TCZ, and 4) longer period of remission before TCZ discontinuation.

## P1-127

### 2 cases of RA patients who had been infected with nontuberculous mycobacteria (NTM) under treatment with Tocilizumab (TCZ), got good clinical course by TCZ re-administration following anti-NTM therapy

Masato Matsushita<sup>1</sup>, Takashi Shimizu<sup>1</sup>, Takuro Nii<sup>1</sup>, Akiko Yura<sup>1</sup>, Satoru Teshigawara<sup>1</sup>, Maiko Yoshimura<sup>1</sup>, Yoshinori Harada<sup>1</sup>, Eriko Tanaka<sup>1</sup>, Soichiro Tsuji<sup>1</sup>, Norihiko Yamaguchi<sup>4</sup>, Yoshihiko Hoshida<sup>5</sup>, Jun Hashimoto<sup>2</sup>, Shiro Ohshima<sup>3</sup>, Yukihiko Saeki<sup>3</sup>

<sup>1</sup>Department of Rheumatology, Osaka Minami Medical Center, Osaka, Japan, <sup>2</sup>Department of Immunological Disorder, Osaka Minami Medical Center, Osaka, Japan, <sup>3</sup>Department of Clinical Research, Osaka Minami Medical Center, Osaka, Japan, <sup>4</sup>Department of Respiratory, Osaka Minami Medical Center, Osaka, Japan, <sup>5</sup>Department of Clinical Examination, Osaka Minami Medical Center, Osaka, Japan

Conflict of interest: None

Biological agents, including IL-6 blocker tocilizumab (TCZ), have had a great impact to the strategy of RA treatment last one decade. However the efficacy of these drugs are already well known, adverse events accompanied with Bio treatment, especially infectious disease has been a matter of concern. Mycobacterium infection is one of the typical opportunistic infections under immune-suppressive status. Risk and prophylaxes against Mycobacterium tuberculosis infection of RA patient with Bio therapy has been established as clinical protocol, on the other hand, little is known about nontuberculous mycobacterium (NTM) infection. Now herein, we report 2 cases of RA patients complicated with NTM during TCZ treatment. And they have successfully re-treated by TCZ following anti-NTM drugs. NTM infection is thought to be a contra-indication of Bio treatment including TCZ according to JCR recommendation. But recently, the clinical guideline by Japanese Respiratory Society propose to consider the use of Bio evaluating both risk and benefit in each cases.

## P1-128

### Short-term results of joint-preserving surgery for forefoot deformity of rheumatoid arthritis

Naoe Tatematsu<sup>1</sup>, Yohei Kawaguchi<sup>1</sup>, Masaki Kobayashi<sup>1</sup>, Hideyuki Goto<sup>1</sup>, Masahiro Nozaki<sup>1</sup>, Hiroto Mitsui<sup>1</sup>, Yuka Mukofujiwara<sup>2</sup>, Takanobu Otsuka<sup>1</sup>, Yuko Nagaya<sup>3</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Nagoya City University, Nagoya, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Kainan Hospital, The Aichi Prefectural Federation of Agricultural Cooperatives for Health and Welfare, Yatomi, Japan, <sup>3</sup>Department of Joint Surgery for Rheumatic Disease, Nagoya City University, Nagoya, Japan

Conflict of interest: None

[Objectives] We report the midterm results of joint preserving surgery for forefoot deformity of rheumatoid arthritis (RA). [Methods] Material included 8 cases 10 feet with RA forefoot deformity whom underwent metatarsal oblique osteotomy reduction surgery at Nagoya City University Hospital between January 2013 and April 2014. All cases were women, average age was 51.6 years (34-77 years), the average follow-up duration was 1.0 years (0.5-1.5 years). The average disease duration was 16.9 years (11-25 years). The average DAS28-CRP was 2.00 (1.15-3.30). Hallux valgus angles (HV angle), first-second metatarsal angle (M1M2 angle), first-fifth metatarsal angle (M1M5 angle) and Foot functional score were measured before surgery, and at the time of final follow-up. [Results] The average HV angle improved 42° to 26.3°. The

average M1M2 angle improved 14.0° to 11.8°. The average M1M5 angle improved 34.8° to 29.5°. Foot functional score improved from before surgery to the time of final follow-up. [Conclusion] All items at the time of final follow-up were significantly more improved than before surgery. So we suppose that SOO is an effective treatment for forefoot deformity of rheumatoid arthritis.

### P1-129

#### Clinical results of surgical treatment for rheumatoid forefoot deformities

Masahiro Horita<sup>1</sup>, Keiichiro Nishida<sup>2</sup>, Kenzo Hashizume<sup>1</sup>, Kenta Saiga<sup>1</sup>, Ryuichi Nakahara<sup>1</sup>, Ryoza Harada<sup>1</sup>, Takahiro Machida<sup>1</sup>, Toshifumi Ozaki<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, <sup>2</sup>Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

Conflict of interest: None

[Objectives] To assess the clinical outcome of surgical treatment for forefoot deformities in patients with rheumatoid arthritis. [Methods] 69 feet of 50 patients underwent surgery on the lesser toe. The mean age at the surgery of the patients who underwent resection arthroplasty (resection group) and sliding oblique osteotomy (joint-preserved group) were 66.8 and 62.2 years, respectively. The average follow-up period was 23.8 and 14.7 months in the resection and the joint-preserved groups, respectively. Pre- and postoperative clinical evaluation included modified HAQ (mHAQ), disease activity (DAS28-CRP), Japanese Society for Surgery of the Foot (JSSF) scale, and postoperative complications. In the joint-preserved group, change of Larsen grade or repair of bone erosions were also assessed. [Results] The mean JSSF scale improved significantly from 59.4 to 88.9 in the resection group and from 63.7 to 91.5 in the joint-preserved group, respectively ( $p < 0.01$ ). In the joint-preserved group, the repair of bone erosion was seen in 6 joints (6.5%) during the follow-up. [Conclusion] Both resection group and joint-preserved group showed good clinical outcomes in the short-term. The joint-preserving surgery should be considered for younger patient with better disease control.

### P1-130

#### A case of hallux valgus deformity after total ankle arthroplasty in patient with RA

Makoto Hirao<sup>1</sup>, Kosuke Ebina<sup>1</sup>, Kenrin Shi<sup>4</sup>, Hideki Tsuboi<sup>2</sup>, Shosuke Akita<sup>3</sup>, Shigeyoshi Tsuji<sup>3</sup>, Hideki Yoshikawa<sup>1</sup>, Jun Hashimoto<sup>2</sup>

<sup>1</sup>Department of Orthopaedics, Osaka University Graduate School of Medicine, <sup>2</sup>Department of Rheumatology, National Hospital Organization, Osaka-Minami Medical Center, <sup>3</sup>Department of Orthopaedics, National Hospital Organization, Osaka-Minami Medical Center, <sup>4</sup>Department of Orthopaedic Surgery and Center for Global Health, Osaka University Hospital

Conflict of interest: None

[Objectives] It has been recognized that hallux valgus (HV) deformity has relationship with hindfoot valgus deformity. In this time, we experienced a case of hallux valgus deformity after total ankle arthroplasty in patient with RA. [Methods/case] Sixty three years old woman with 31 years history of RA (stage IV, class II) suffered from ankle destruction with 11 degrees varus deformity of hindfoot. TAA was performed with adequate correction of ankle/hindfoot. Within 3 years after TAA, HV deformity had appeared and promoted, subsequently showed 42 degrees of HV angle. [Results/Conclusion] Retrospectively, opposite side of foot was observed. It showed 3 degrees of varus hindfoot (mild), at the same time HV deformity already appeared (HV angle: 36 degrees). After several years, HV surgery was required. It is considered that severe varus hindfoot has a possibility to mask the HV deformity because of lateral ray loading, and hindfoot valgus correction after TAA lead to promote 1<sup>st</sup> ray loading, subsequently HV deformity would appeared. This case would give us an important information that adequate correction of varus hindfoot has a possibility to cause forefoot HV deformity.

### P1-131

#### Metatarsal joint fusion in patients with Rheumatoid Arthritis (RA) using Synthes X-Plate®

Kosuke Okuda, Hiroshi Okubo, Tsukasa Matsubara  
Matsubara Mayflower Hospital

Conflict of interest: None

[Objectives] RA patients can have inflammation and destruction on the metatarsal (talo-navicular, calcaneo-cuboidal) joints. Many surgical approaches have been reported on fusion of the joints. But, if fixation is weak, the duration of immobilization and non-weight bearing have to be longed. Synthes X-Plate® is the device for the treatment to small bones or joints, and including locking plate system. [Methods] We have done on 5 RA patients. Plaster slab was applied to immobilize after the surgery. After 4 weeks of the immobilization, partial weight bearing was started. [Results] The operation was done in five patients with RA. All were female, the disease duration was 3-30 years (avg. 12.6 yrs), preop. SDAI was 3.6-20.7 (avg. 13.5), preop. AOFAS score was 39-87 points (avg. 58.4). 4 cases were done on both TN and CC joints, one was only on TN joint. The follow-up duration was 30 to 39 months (avg. 33.6 mos). All patients decreased their pain. The bone union was completed. Only one patient had to get the removal of the plate because of skin pain. Postop. AOFAS score was 39-100 (avg. 77.6). [Conclusion] We used X-Plate® for the fusion of metatarsal joints on the patients with RA. All patients could decrease their pain, the bone union was completed.

### P1-132

#### Result of surgical treatment for infected implant arthroplasty of great toe, with resection arthroplasty of the other toe for Rheumatoid Arthritis for foot deformity

Hiroshi Okubo, Kosuke Okuda, Tsukasa Matsubara  
Matsubara Mayflower Hospital

Conflict of interest: None

[Objectives] We experienced 5 cases of infected implant arthroplasty of Great Toe with resection arthroplasty of the other toe for rheumatoid arthritis for foot deformity. [Methods] Between 2004 June and 2014 June, We performed 119 cases (189 feet) swanson implant arthroplasty of great toe with resection arthroplasty of the other toe for RA patient. We diagnosed infection by Guideline of Infectious Disease Society of America (2013). [Results] The average age of the patient at the time of infection was 59.6 years (range 40-77). All patients were women. The average of the C-reactive protein determination was 0.63 (0.08, 0.8, 0.2, 0.47, 1.6). On the big toe, the condition of skin was following, fistel two cases, defect one cases. The result of culture of fluid was following, S.aureus 1 case, corynebacterium 1 case, M.R.S.A 1 case, negative 1 case. Operative debridement was performed at all cases. The cases of resection arthroplasty was four, and arthrodesis was performed at one case. The average duration of postoperation was 33.8M (4-71). [Conclusion] The case of recurrence was none.

### P1-133

#### Methicillin-resistant staphylococcus aureus (MRSA) infection in RA knee joint treated with direct intraarticular antibiotic infusion: a case report

Junichi Fujisawa<sup>1</sup>, Naoki Kondo<sup>2</sup>, Naoko Kudo<sup>2</sup>, Naoto Endo<sup>2</sup>, Katsumitsu Arai<sup>3</sup>

<sup>1</sup>Carrier Support Center for Resident, Niigata University Medical and Dental Hospital, Niigata, Japan, <sup>2</sup>Division of Orthopedic Surgery, Department of Regenerative and Transplant Medicine, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, <sup>3</sup>Division of Orthopedic Surgery, Niigata Prefectural Central Hospital, Niigata, Japan

Conflict of interest: None

[Objectives] To report a case of deep MRSA infection in knee joint and could be suppressed by treating with the direct intraarticular antibiotic infusion via catheter. [Case] An 81-year-old female patient developed rheumatoid arthritis (RA) and had caught MRSA infection in her right knee joint three years ago. Finally infection had been suppressed with us-



ing vancomycin pregated cement beads technic. Three years later, she caught infection again in her right knee and we tried to perform the vancomycin pregated cement beads technic again. However, this time the infection could not be suppressed. So we tried to treat with direct intra-articular antibiotic infusion via catheter. Two Hickman catheters were introduced to her right joint space and performed intraarticular infusion of vancomycin via the catheter once or twice daily for 8 weeks. Dose of vancomycin was adjusted according to the vancomycin trough levels. The infection was suppressed and did not occur again until seven months after the operation. The serum vancomycin level could be detected until 5 months after the operation. [Conclusion] It is useful to control deep MRSA infection in knee joint by treating with the direct intraarticular antibiotic infusion via catheter.

### P1-134

#### The treatment of infection after total knee arthroplasty in rheumatoid arthritis patients

Atsushi Narita<sup>1</sup>, Yuya Takakubo<sup>1</sup>, Akiko Sasaki<sup>1</sup>, Hiroshi Oorii<sup>2</sup>, Ichizo Asahina<sup>3</sup>, Mitsuhiro Hariu<sup>4</sup>, Michiaki Takagi<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Yamagata University Faculty of Medicine, <sup>2</sup>National Hospital Organization Yamagata National Hospital, <sup>3</sup>Yamagata Prefectural Central Hospital, <sup>4</sup>Nihonkai General Hospital, <sup>5</sup>Yamagata Saisei Hospital

Conflict of interest: None

[Objective] To evaluate the clinical results of infected total knee arthroplasties (TKAs) in rheumatoid arthritis (RA) patients at our institution. [Methods] From April 2004 to March 2013, we retrospectively evaluated 368 TKAs in RA patients. [Results] Seven patients presented with an infection (infection rate: 1.4%). There were 5 cases of infection after primary TKA. The infection onset was within 1 year in 1 case (20%), within 2 years in 2 cases (40%), and after 2 years in 2 cases (40%). All the patients had a type III infection (acute hematogenous) according to the Segawa classification. No cases revealed loosening on x-ray. Four patients underwent open debridement, and 4 underwent arthroscopic debridement (AD). Six patients had successful implant retention. However, AD in one patient failed, and two-stage revision was required. The rate of implant retention was 86%. Resistant microorganisms were not detected in the successful implant retention cases. [Conclusions] The infection rate in our study is comparable to that previously reported. Of the implants, 86% were successfully retained. Thus, early open debridement or AD is important for implant retention. In addition, the infection onset after 1 year was 80%, suggesting that careful follow-up is needed in RA patients.

### P1-135

#### Case reports of pseudogout attack after total knee arthroplasty

Yuki Etani, Masataka Nishikawa, Shoichi Kaneshiro, Hajime Owaki  
Japan Community Health Care Organization Osaka, Osaka, Japan

Conflict of interest: None

[Purpose] There are few reports of pseudogout attack (PA) as a complication of total knee arthroplasty (TKA). We report two cases that suffered PA in early postoperative period. [Case 1] A 73-years-old, woman suffered bilateral osteoarthritis (OA) of the knee, and we performed right TKA. Postoperative course was general good. On the 13th day after surgery, however, she suffered fever and right knee pain. In blood test, WBC rose to 9300, CRP rose to 20.21mg/dL. We punctured the right knee joint, and synovial fluid was yellow and cloudy. No bacterium was detected in the fluid by gram staining, however, CPPD crystals was done. We diagnosed as PA. Treatment with NSAIDs improved clinical symptoms, and inflammatory reaction got negative. [Case 2] A 75-years-old, woman suffered bilateral OA of the knee, and we performed right TKA. Postoperative course was general good. But on 19th day, she suffered from PA on her right knee. The treatment with puncture and NSAIDs improved PA. [Discussion] The etiology of these PA are not clarified, but both cases could be treated with NSAIDs and drainage of synovial fluid. PA produce manifestations similar to septic arthritis's. Therefore, we should check not only bacterium but also CPPD crystals when symptoms of fever up or knee pain appear.

### P1-136

#### The effect of total knee arthroplasty on the arthritis of other joints in patients with rheumatoid arthritis

Yukio Yonemoto, Koichi Okamura, Chisa Okura, Tetsuya Kaneko, Takahito Suto, Tsutomu Kobayashi, Kenji Takagishi  
Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine

Conflict of interest: None

[Objectives] The aim of this study was to assess the arthritis of systemic large joints at baseline and 12 weeks after TKA using 18FDG-PET (PET)/CT in patients with RA. [Methods] Seventeen RA patients who underwent TKA were included this study. We assessed the FDG-PET, CRP, ESR, MMP-3, DAS28-ESR, DAS28-CRP, CDAI, SDAI, HAQ-DI, HSS score and Knee ROM at baseline (just before TKA) and 12 weeks after TKA. [Results] The median age of the patients was 68 years old, and the disease duration was 23 years. Concomitant MTX and PSL treatment was being administered to 71% of the patients. One patient was treated with infliximab, two used etanercept, one used tocilizumab and two used abatacept. The CRP, MMP-3, all of the composite measurements, the HAQ and the knee function improved significantly 12 weeks after TKA. These data show the changes in the SUV of each joint. The SUV of the bilateral wrist joints decreased significantly 12 weeks after TKA. However, the SUV of other large joints were unchanged. [Conclusion] TKA can improve not only the ADL and knee function, but also the disease activity in RA patients. However, TKA has limited effectiveness against the arthritis of the joints not undergoing surgery.

### P1-137

#### Long-term results of Hy-Flex II TKA

Hiroshi Nakamura<sup>1</sup>, Toshikazu Kamada<sup>2</sup>, Masahito Koiwa<sup>3</sup>, Kenji Takahashi<sup>1</sup>, Akiko Sato<sup>1</sup>, Hidemi Kawaji<sup>1</sup>, Shinro Takai<sup>1</sup>  
<sup>1</sup>Department of Orthopaedics, Nippon Medical School, <sup>2</sup>Hara Orthopedic Hospital, <sup>3</sup>Department of Orthopedics, Shuuwa General Hospital

Conflict of interest: None

[[Objectives] Long-term results of Hy-Flex II total knee arthroplasty (TKA) that was designed as cruciate retaining (CR) type prosthesis in Japan were investigated. [Methods] Cases of Hy-Flex II TKA followed-up more than 10 years were identified in the medical record. The survival rate was analyzed with a Kaplan-Meire method with the time of joint removal as the end point. Clinical findings and radiological findings were also studied. [Results] 103 patients with 136 knee joints were identified. An average follow-up period was 13.0 years (10-17 years) and a follow-up rate was 60.3%. JOA and HSS scores have kept improved. An average flexion was 119.5 degrees. Revision surgery was undergone in 9 joints including 7 HDP exchange. The survival rates at 10 and 15 years were 97.8% and 92.3% respectively and the rates were significantly low in OA. No loosening was observed except for joints that needed component revision. [Discussion and Conclusion] Hy-Flex II TKA showed excellent long-term clinical results. However, HDP wear was frequently found. One of the reasons was high mobility that caused high strain on joint surface. Another reason was that the knee with severe destruction should be reconstructed with CR type prosthesis.

### P1-138

#### The impact of disease activity and glucocorticoids on bone density in rheumatoid arthritis

Tatsuo Watanabe<sup>1,2</sup>, Toshihisa Kojima<sup>1</sup>, Nobunori Takahashi<sup>1</sup>, Koji Funahashi<sup>1</sup>, Shuji Asai<sup>1</sup>, Toki Takemoto<sup>1</sup>, Kenya Terabe<sup>1</sup>, Yutaka Yoshioka<sup>1</sup>, Nobuyuki Asai<sup>1</sup>, Naoki Ishiguro<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Nagoya University School of Medicine, Nagoya, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Yoneda Hospital, Nagoya, Japan

Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) is a chronic inflammatory disease, cause joint destruction and osteoporosis. In addition, glucocorticoids use cases not a few. The impact of disease activity and glucocorti-

coids use on bone metabolism markers and bone mineral density (BMD) were investigated [Methods] 107 female RA patients were studied retrospectively. DEXA method BMD of the lumbar spine and femoral neck were measured 2 years. [Results] There were two cases of DAS28-CRP  $\geq 2.7$  group (HM group) and one case of DAS28-CRP  $< 2.7$  group (L group) osteoporosis-related fractures. There was no significant difference between both group lumbar spine BMD changes, but femoral neck BMD of the HM group decreased. There was no significant difference in TRACP-5b value. 24 cases fulfill the guidelines on the management and treatment of glucocorticoid-induced osteoporosis 2014, drug therapy has been performed in 11 cases. There was no significant difference in lumbar spine BMD change in the 24 cases, but femoral neck BMD decreased. [Conclusion] Disease activity of RA, and glucocorticoid use had an impact on the femoral neck BMD. Appropriate drug therapy is important for glucocorticoids use cases

### P1-139

#### Factors influencing vertebral and femoral bone mineral density in patient with rheumatoid arthritis (RA)

Takayuki Wakabayashi<sup>1</sup>, Naofumi Chinen<sup>1</sup>, Yasuo Suzuki<sup>2</sup>

<sup>1</sup>Division of Rheumatology, Tokai University Hachioji Hospital, Tokyo, Japan, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Tokai University School of Medicine, Kanagawa, Japan

Conflict of interest: None

[Objective] Bone loss is common in RA due to the effect of the disease and/or some of its medications such as corticosteroids. In the last 15 years, the early use of methotrexate (MTX) and biologics has changed the natural course of the disease. The aim of the study is to clarify the prevalence of osteoporosis and various factors affecting the vertebral and femoral bone loss in RA patients. [Methods] Thirty-five RA patients (9 men and woman 26) were subjected to measure lumbar and femoral bone mineral density (BMD) by DEXA and investigated the contributing factors to bone loss. [Results] The average age was 66.4 years old. MTX was given in more than 80% of cases. The mean lumbar and femoral BMD were 90.9% and 89.8%, respectively in the female patients, loss of femoral BMD was higher than that of lumbar. Femoral and vertebral bone loss less than 70% from YAM was identified in only 10% or less in female RA patients. Elevation of serum TRACP-5b was found in 63.6% of patients who showed bone loss. There was no association between bone loss and disease activity. [Conclusion] The prevalence of osteoporosis in RA patients did not differ from the general prevalence. Elevation of serum TRACP5b was one of the predictors for generalized bone loss in RA.

### P1-140

#### Predictability of joint destruction by bone mineral density in the early stage of rheumatoid arthritis

Hiromu Ito<sup>1</sup>, Takahiro Iwata<sup>1</sup>, Moritoshi Furu<sup>1,2</sup>, Motomu Hashimoto<sup>2</sup>, Takao Fujii<sup>2,3</sup>, Masahiro Ishikawa<sup>1,2</sup>, Noriyuki Yamakawa<sup>3</sup>, Tsuneyo Mimori<sup>2,3</sup>, Shuichi Matsuda<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Kyoto University Graduate School of Medicine, <sup>2</sup>Department of the Control for Rheumatic Diseases, Kyoto University Graduate School of Medicine, <sup>3</sup>Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine

Conflict of interest: Yes

Objective: to investigate the relationship between osteoporosis and joint destruction and the predictability of the latter by the bone marrow density in the early stage of rheumatoid arthritis. Methods: Thirty three female patients with rheumatoid arthritis within two years of the duration of the disease were included in this study. The average of age, the duration of the disease, and the BMI were 58.6, 0.97, and 21.7, respectively. The BMD of the distal radius and the proximal femur was obtained by DEXA and was evaluated by YAM. Results: The averages of DAS28-ESR, HAQ-DI, and modified total Sharp score (mTSS) were 2.78, 0.42, and 21.7, respectively. MTX was used in 90.9% of patients, and the average dose was 8.1mg. Oral steroid was used in 39.8%, and the average dose was 4.6mg. BMD of the radius was significantly correlated with

age, ESR, DAS28-ESR, and mTSS, and that of the femur was correlated with BMI and mTSS. Five variates of age, DAS28-ESR, BMD of the femur, that of the radius, and SDAI can partially predict mTSS ( $R^2=0.5879$ ). Conclusion: In the early stage of rheumatoid arthritis, BMD of the radius and the femur can partially predict joint destruction.

### P1-141

#### Atypical femoral fractures in rheumatic patients

Yuya Takakubo<sup>1</sup>, Shota Okuda<sup>1</sup>, Ryuta Ohishi<sup>1</sup>, Yasushi Naganuma<sup>1</sup>, Hiroharu Oki<sup>1</sup>, Tomoyuki Hirayama<sup>1</sup>, Kan Sasaki<sup>1</sup>, Atsushi Narita<sup>1</sup>, Suran Yang<sup>1,3</sup>, Akiko Sasaki<sup>1,3</sup>, Hiroko Sato<sup>2</sup>, Kazuko Suzuki<sup>2</sup>, Kazunobu Ichikawa<sup>2</sup>, Tsuneo Konta<sup>2</sup>, Michiaki Takagi<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Yamagata University Faculty of Medicine, <sup>2</sup>Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, Yamagata, Japan, <sup>3</sup>Yoshioka Hospital

Conflict of interest: None

[Objectives] The purpose of this study is to analysis the atypical femoral fractures in rheumatic patients in our institutes retrospectively. [Methods] We investigated the cases of atypical femoral fractures among 1,298 rheumatic patients. [Results] The patients with atypical femoral fractures were 4 limbs in three women (0.2 %). The mean ages was 64 year-old (51-72). As comorbid conditions, two patients has dermatomyositis, one rheumatoid arthritis and one polyarteritis nodosa. Fracture types were three subtrochanteric and one diaphyseal femoral fractures. All patients received bisphosphonates (BPs) and prednisolone (PSL). Mean duration of receiving the drugs was 75 months (48-120) and 82 months (60-82), respectively. After affecting the fractures, BPs were quitted and the surgery using intramedullary nail fixation were performed in all cases. Teriparatide was induced and therapy of low-intensity pulsed ultrasound was started for all cases after healing their wounds. Mean duration of post-operative observation was 8 months (3-15). All of them have been observed the delayed union of fracture site at their latest follow-up. [Conclusion] We concluded the careful treatment and observation for the therapy of atypical femoral fractures were needed even after the surgery.

### P1-142

#### Atypical femoral fractures in patients with rheumatoid arthritis

Yukio Esaki<sup>1,2</sup>, Hiroataka Iura<sup>1,2</sup>, Kenjiro Fujimura<sup>3</sup>, Satoshi Kamura<sup>1,2</sup>, Koji Sakuraba<sup>1,2</sup>, Masanari Ota<sup>1,2</sup>, Goh Hirata<sup>1,2</sup>, Hisaaki Miyahara<sup>1,2</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Kyushu Medical Center, National Hospital Organization, Fukuoka, Japan, <sup>2</sup>Clinical Research Institute, Kyushu Medical Center, National Hospital Organization, Fukuoka, Japan, <sup>3</sup>Department of Orthopaedic Surgery, Kyushu University, Fukuoka, Japan

Conflict of interest: None

[Objectives] We research and report about the atypical femoral fractures occurred in patients with rheumatic diseases who were diagnosed and treated in our hospital. [Methods] We have treated five patients with rheumatic diseases who had atypical femoral fractures since January 2011. One patient was a man with the bilateral fractures who had been suffering from Behcet's disease, and four were women with rheumatoid arthritis. The average age of onset of the fractures was 60.4 years (48-66years). All of them had subtrochanteric or shaft fractures of the femur with no or minimal trauma. [Results] All patients had long-term use of steroid (average dose of 7.6mg) and bisphosphonate. The average period was five years and six months from the start of the oral medication of bisphosphonate to the onset of the fractures. All of the fractures were fixed with intramedullary nail. Three patients with incomplete fractures had progression to complete fractures in the conservative therapy or waiting time for the operation. It was suggested that conservative treatment of atypical femoral fracture was less effective. [Conclusion] Prophylactic intramedullary fixation was recommended for atypical femoral insufficiency fracture.

### P1-143

#### A case of femoral neck fracture with minor trauma using bisphosphonate bisphosphonate

Ryo Date, Takatomo Mine

National Hospital Organization Kanmon Medical Center

Conflict of interest: None

We report a case of femoral neck fracture that was so similar atypical femoral fracture. 79 years old woman felt right hip pain without accident. Although she had a medical examination, was not diagnosed hip fracture. After one week, she felt severe pain at right hip again with keeping her feet when she stumbled and nearly fall. She was diagnosed right femoral basal-neck fracture after transporting our hospital. She used weekly bisphosphonate (BP) in 4 years. Post injury four days, we performed osteosynthesis by CHS. We prescribed daily teriparatide in two weeks later after surgery, and although starting full weight bearing in six weeks later, fracture is not union yet at twenty-four weeks. We considered this fracture was very similar AFF because using BP long term, showing short and not comminuted fracture, cortical thickness etc. We must plan BHA or THA when bone union will not success.

### P1-144

#### Evaluation about subsequent changes of bone turnover markers and bone mineral density by treatment using denosumab in postmenopausal women with osteoporosis and osteopenia

Naohiro Asada

Municipal Tsuruga Hospital, Tsuruga, Fukui, Japan

Conflict of interest: None

**[Objectives]** We estimated the efficacy of treatment by naïve or second-line use of denosumab in women with osteoporosis and osteopenia. **[Methods]** 45 women with osteoporosis and osteopenia were treated by denosumab. The average of the age was 71.8 years old. 14 patients with RA were included in this study. 11 patients were naïve, and 34 patients were switched. Subsequent changes of serum values in NTX, TRACP-5b, PINP, ucOC, and homocysteine were examined. The bone mineral density of lumbar spines, femoral cervical neck and/or radius was analyzed both at the initial screening and 6 months later in each patients. **[Results]** The mean value of serum NTX, PINP and ucOC was gradually reduced. The mean value of serum TRCP-5b was unique, which was usually inhibited at 1 month later after each treatment by denosumab. The mean value of serum homocysteine was always maintained within the normal range. The bone mineral density of lumbar spines especially achieved increase of 3.9% at 6 months later after denosumab. Otherwise, that of femoral cervical neck and radius was not significantly increased. The bone mineral density of lumbar spines in patients with RA was also increased. **[Conclusion]** Treatment by denosumab was effective in women with osteoporosis and osteopenia, including RA.

### P1-145

#### Effects of denosumab on bone mineral density and bone turnover in osteoporosis in rheumatoid arthritis patients

Ichiro Nakamura<sup>1,2</sup>, Takuo Juji<sup>2</sup>, Kensuke Kawabata<sup>2</sup>, Katsumi Ito<sup>2</sup>

<sup>1</sup>Faculty of Medical Science for Health, Teikyo Heisei University, <sup>2</sup>Department of Rheumatology, JCHO Yugawara Hospital

Conflict of interest: None

**[Objectives]** Osteoporosis is frequently associated with rheumatoid arthritis (RA). Osteoporosis in RA could cause the vertebral fractures and femoral neck fractures, causing decreases in activities of daily living in RA patients. The purpose of this study is to examine the effects of denosumab, RANKL inhibitor, on bone mineral density (BMD) and bone turnover in osteoporotic RA patients. **[Methods]** RA patients received subcutaneous denosumab (60 mg) injection (n=43; mean age, 69.2; mean duration of RA, 21.5 years). Mean values of %YAM (young adult mean) are 63.2% and 72.6% in femoral neck and lumbar spine, respectively. Assessments included dual x-ray absorptiometry scans of the lumbar spine and femoral neck, and levels of serum procollagen 1N-terminal peptide (PINP) and tartrate-resistant acid phosphatase 5b (Tracp5b) at baseline

and 6 months after treatment. **[Results]** Denosumab treatment significantly increased BMD in lumbar spine and femoral neck. Denosumab also markedly suppressed both bone formation marker (PINP) and bone resorption marker (Tracp5b). **[Conclusion]** These results suggest that denosumab increases BMD and reduces bone turnover in osteoporotic RA patients and may provide a new therapeutic option for reducing systemic bone loss in osteoporosis associated with RA.

### P1-146

#### Efficacy of denosumab in patients with systemic autoimmune diseases

Kotaro Shikano, Kaichi Kaneko, Mai Kawazoe, Shotaro Masuoka, Hiroshi Sato, Emiko Shindo, Natsuki Fujio, Makoto Kaburaki, Sei Muraoka, Nahoko Tanaka, Tatsuhiko Yamamoto, Tomoko Hasunuma, Shinichi Kawai  
Division of Rheumatology, Department of Internal Medicine, School of Medicine, Faculty of Medicine, Toho University

Conflict of interest: None

**[Object]** Denosumab, anti-receptor activator nuclear factor κB ligand monoclonal antibody, was reported to be superior to other drugs for osteoporosis. This observational study was conducted to clarify the efficacy of denosumab in patients with systemic autoimmune diseases. **[Method]** Serum levels of bone turnover markers and lumbar bone mineral density (BMD) in 12 patients with systemic autoimmune diseases [mean age 70.6±8.3 (S.D), male 1/postmenopausal female 11] at baseline and 6th month after denosumab therapy. **[Result]** Serum levels of NTX (18.6±4.2→15.2±6.0 nmolBCE/L) and TRACP-5b (335.5±236.1→138.3±87.3 mU/dL) were significantly decreased. Serum levels of PINP (34.5±12.6→17.4±9.3 µg/L) and BAP (12.8±4.39→9.46±2.42 µg/L) were also significantly decreased. BMD was significantly increased by 4 percent in comparison with that at baseline after denosumab (0.718±0.094→0.746±0.097 g/cm<sup>2</sup>). On the other hand, BMD in 3 of 12 patients were decreased. These patients who resistant to denosumab had trend of aged cases and lower BMD at baseline. Two of them had received PTH therapy with or before denosumab. **[Conclusion]** In this study, denosumab was effective in systemic autoimmune diseases, however, 25 percent patients were resistant to this treatment. Background of these findings will be discussed.

### P1-147

#### Clinical evaluation of Osteoporosis in Rheumatoid Arthritis patients

Toshiharu Okuda

Okuda orthopedic Clinic, Ogaki, Japan

Conflict of interest: None

The bone mineral density (BMD) of the lumbar spine and femoral neck was measured in 129 patients of Rheumatoid arthritis (RA). For biochemical markers of bone, tartrate-resistant acid phosphatase-5b (TRACP 5b) and bone-type alkaline phosphatase (BAP) in serum. were measured for selecting drugs of osteoporosis. 82 RA patients (mean age 68.9 years old) were diagnosed as osteoporosis according to BMD, and treated with several drugs of osteoporosis, (Vitamin D3 65cases, Bisphosphonate 47cases, Teriparatide 28cases, and Denosmab cases. etc) To prevent osteoporosis in RA, it seems to be not only important to treat RA as good control but also to administer appropriate therapy of osteoporosis in same time.

### P1-148

#### Whether Rheumatoid arthritis(RA) is a risk factor in Rehabilitation or not

Yasuko Hirai<sup>1</sup>, Atsushi Taguchi<sup>3</sup>, Hiroshi Enomoto<sup>4</sup>, Tomoki Origuchi<sup>5</sup>, Atsushi Kawakami<sup>1</sup>

<sup>1</sup>Department of Immunology and Rheumatology, Nagasaki University School of Medicine, Nagasaki, Japan, <sup>2</sup>Department of Macroscopic Anatomy, Nagasaki University Graduate School of Biomedical Sciences, <sup>3</sup>Medical Corporation Wajinkai, Wajinkai Hospital, <sup>4</sup>Enomoto Orthopedic Clinic, <sup>5</sup>Division of Physical Therapy, School of Health sciences, Nagasaki University

Conflict of interest: None

**[Objective]** To exam whether rheumatoid arthritis obstruct treatment and outcome at the rehabilitation. **[Methods]** Subjects were 1519 inpatients admitted to recovery phase rehabilitation wards between April 2010 and March 2010. Patients were divided if they had got RA or not. About the main disease, age, sex, motor/cognitive subscales of functional independence Measure (FIM) calculated score at admission from that at discharge, I extracted rheumatoid arthritis patients and compared with the non RA patients. **[Results]** RA patients were 37 during a period. 25 people (67.6%) suffered from a bone fracture and joint damage. 6 patients (16.2%) suffered from cerebrovascular disorder, and disuse atrophy was suffered 6 (16.2%). The average age of them was 72.4 y.o, Sex average was 1: 4.1. The average of FIM of hospitalization was 84.8 points, and a discharge's point were 99.2. Non RA were 1482 people. 923 (62.3%) suffered from orthopedic disease, 392 patients (26.4%) were cerebrovascular disorder, and disuse atrophy was 167 patients (11.3%). The average age was 74.3 sex average was 1: 1.6. The average of FIM, of hospitalization was 71.5, and a discharge's point were 86.5. **[Conclusion]** Compared with non RA patients, RA was not identified as the protraction factor of the rehabilitation

### P1-149

#### The present situation of rehabilitation for rheumatoid arthritis (AORA registry)

Yusuke Sugimura<sup>1</sup>, Seiya Miyamoto<sup>2</sup>, Natsuo Konishi<sup>4</sup>, Takeshi Kashiwagura<sup>5</sup>, Naohisa Miyakoshi<sup>3</sup>, Yoichi Shimada<sup>3</sup>

<sup>1</sup>South Akita Orthopedic Clinic, Akita, Japan, <sup>2</sup>Department of Orthopedic Surgery, Nakadori General Hospital, Akita, Japan, <sup>3</sup>Department of Orthopedic Surgery, Akita University Graduate School of Medicine, Akita, Japan, <sup>4</sup>Department of Orthopedic Surgery, Akita Kousei Medical Center, Akita, Japan, <sup>5</sup>Department of Rehabilitation Medicine, Akita City Hospital, Akita, Japan

Conflict of interest: None

[Objectives] Rehabilitation is one of the pillars of the treatment of the rheumatoid arthritis (RA). It is said that rehabilitation for the patients with RA is effective to obtain a functional improvement in patients with RA which do not compensate the medication. We investigated the present situation of rehabilitation for the patients with RA. [Methods] In Akita orthopedic group on rheumatoid arthritis (AORA registry), We investigated the number of rehabilitation prescription for the patients with all disease and for the patients with RA from 2010 to 2013. [Results] The numbers of rehabilitation prescription for the patients with RA were 109 (2010), 133 (2011), 181 (2012) and 225 (2013). The percentage of patients with RA accounted for patients with all disease were 2.5% (2010), 2.5% (2011), 3.2% (2012) and 4.1% (2013). [Conclusion] The percentage of patients with RA accounted for patients with all disease had increased from after the establishment of AORA registry. Many of the reasons why the patients don't do rehabilitation is because there is no explanation or guidance from a doctor. We need to be aware of the importance of rehabilitation for the patients with RA.

### P1-150

#### Three cases of home recovery from severe connective tissue disease made possible by inter-hospital cooperation (Approaches to rehabilitation following acute phase treatment)

Hiroshi Tsushima<sup>1,2</sup>, Yoshihiro Ishihara<sup>1</sup>, Sadanobu Katsube<sup>1</sup>, Yoshinari Takasaki<sup>2</sup>, Masahiko Yasuda<sup>1</sup>

<sup>1</sup>Rehabilitation Nakaizu Spa Hospital, Shizuoka, Japan, <sup>2</sup>Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Background] Heavy treatments like steroid pulse, high-dose steroids, and immunosuppression are often needed in primary treatment of connective tissue disease; lengthy hospitalization can be required. Such therapies, their complications, and disuse syndrome make many patients hard to discharge; but long-term hospitalization is a major cause of bed shortages at acute care hospitals. Proactive, fast intervention on rehabilitation transfer and hospital discharge support is needed. [Methods] We received 3 severe cases (SLE=1, PM=1, SLE+PM overlap=1) who could

not be discharged due to low ADL during heavy initial therapy and complications at acute care hospital. We conducted rehabilitation and continuous intervention treatment, and checked clinical courses, and the social role our hospital played. [Results] We compared ADL in each cases from admission and discharge, and found improvement in the Barthel Index, 10m walk test, and FIM score. We checked activity in the primary diseases, and gave medical intervention. We saw no flare-ups in any of the primary diseases. [Conclusion] Discharge support and transfer for early rehabilitation may allow smoother home recovery in cases of delayed primary treatment and for patients with severe connective tissue disease and serious complications.

### P1-151

#### Study of antiphospholipid syndrome associated with cutaneous vasculitis

Kazuo Takahashi<sup>1,2</sup>, Miwa Kanaoka<sup>2</sup>, Rika Okada<sup>2</sup>, Michiko Aihara<sup>2</sup>, Yukie Yamaguchi<sup>2</sup>

<sup>1</sup>Dept. of Dermatology, Fujisawa City Hospital, <sup>2</sup>Dept. of Dermatology, School of Medicine, Yokohama City University

Conflict of interest: None

[Objectives] Antiphospholipid syndrome (APS) is an autoimmune hypercoagulable state caused by antiphospholipid antibodies. APS provokes blood clots in both arteries and veins as well as pregnancy-related complications such as miscarriage, stillbirth, preterm delivery. We have recently encountered with 5 APS associated with cutaneous vasculitis. We studied whether they had new clinical entity between APS and vasculitis. [Methods] All 5 cases met the diagnostic criteria for APS and histologically had vasculitis (age: 18-72, all female). [Results] Cutaneous finding had indurative erythema with tenderness in all cases. 5 cases had a prolonged aPTT and positive lupus anticoagulant. None of them had anticardiolipin antibodies including anti CL/ $\beta$ 2GP I antibody. 1 hypocomplementemia was detected. No cerebrocardiological events had been seen. 3 cases were detected lacunar infarction, 1 case was detected retinal artery occlusion. Histopathological findings was so called lymphocytic vasculitis, not Leukocytoclastic vasculitis in deep dermis and subcutaneous layer. [Conclusion] Although it is still unclear whether APS associated with vasculitis had a specific entity, they have a curious issue in that APS is accompanied with inflammation. Therefore further studies should be required.

### P1-152

#### The background of SLE patients who received a renal biopsy

Atsushi Saito, Yuichi Yokoyama, Takeo Abe, Tetsuya Furukawa, Takahiro Yoshikawa, Takuya Hino, Aki Nishioka, Masahiro Sekiguchi, Naoto Azuma, Masayasu Kitano, Shinichiro Tsunoda, Kiyoshi Matsui, Hajime Sano

Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine

Conflict of interest: None

[Objectives] The aim of the present study was to evaluate the background of SLE patients who had a renal biopsy. [Methods] We performed a retrospective study of 36 SLE patients (32 females and 4 males) who received a renal biopsy in our hospital from 2011 to 2014. [Results] Baseline characteristics of the 36 patients were: Age: 38.6 $\pm$ 13.3years, PSL: 15.9 $\pm$ 5.9mg/day (PSL free: 9), Combination of immunosuppressant (TAC: 10, MZR: 6, CyA: 5, AZA: 1, overlap: 3), Nephrotic syndrome: 28%, Positive rate of spot proteinuria: 88.9%, Positive rate of microscopic hematuria: 44.4%, Positive rate of urinary deformed RBC: 44.4%, Positive rate of abnormal urinary cast: 61.1%, Proteinuria: 3.1 $\pm$ 4.2g/day, Urinary  $\beta_2$ MG: 3176 $\pm$ 6560 $\mu$ g/l/day, Urinary NAG: 9.7 $\pm$ 12.9U/l/day, Albumin: 3.0 $\pm$ 0.7g/dl, Cr: 0.9 $\pm$ 0.6mg/dl, C3: 63.6 $\pm$ 28.9mg/dl, C4: 11.1 $\pm$ 6.9mg/dl, Anti ds-DNA Ab: 224 $\pm$ 508IU/l. According to 2003 ISN/RPS classification, we classified all renal biopsies as class I: 0, class II: 1, class III: 2, class IV: 20, class V: 0, VI: 1, class III+V: 2 and class IV+V: 10. [Conclusion] Even SLE patients with minimal abnormality of urinary findings, renal biopsy findings showed more than expected in the active glomerular changes and advanced glomerular sclerosis. Therefore it should be performed actively renal biopsy in early. In addition we present

clinical course and treatment after renal biopsy.

### P1-153

#### Disease activity and fetal safety of pregnant 10 cases with rheumatic disease

Eiko Miyagawa, Ayako Fujimoto, Komei Sakata, Mikako Iwakura, Koyu Hoshino, Shinya Hirata

Department of Rheumatology and Clinical Immunology, Kumamoto University Hospital, Kumamoto, Japan

Conflict of interest: None

[Objectives] Rheumatic diseases often affect young women in the reproductive age. It is unknown how pregnancy and delivery affects disease activity. [Methods] We analyzed 10 pregnant cases of 7 patients with rheumatic disease. [Result] Mean age at disease onset was 26 ys old, and 31 ys old at pregnancy. Out of 10 cases, 3 cases were adult onset still disease (AOSD), 2 were systemic lupus erythematosus (SLE), 2 were mixed connective tissue disease (MCTD), 2 were systemic sclerosis and 1 was dermatomyositis. Four cases were anti-SSA Ab positive, and 1 was lupus anticoagulant-positive. At onset of pregnancy, prednisolone was used in 9 cases (mean 6mg/day), azathioprine and tacrolimus in 2 cases each, and cyclosporine and mizoribine in 1 case each. Six cases gave full term birth, 3 had spontaneous abortion at first trimester, and 1 had artificial abortion. Disease exacerbation was seen in 1 case (AOSD) at first trimester, 2 cases (SLE, AOSD) at last trimester, and 2 cases (AOSD, MCTD) after delivery. Any cases could maintain pregnancy to intensify treatment. Among neonate, 2 low birth weight cases and a neonatal jaundice were cured in pediatrics ward. [Conclusion] Pregnant women with rheumatic diseases should be managed by careful observation of disease activity and baby.

### P1-154

#### The levels of anti-C1q antibodies fluctuated along with the state of hypocomplementemic urticarial vasculitis associated with systemic lupus erythematosus: A case series report

Kumiko Saka<sup>1</sup>, Kohei Miyake<sup>2</sup>, Daisuke Hoshi<sup>1</sup>, Yuko Okamoto<sup>1</sup>, Masanori Hanaoka<sup>1</sup>, Tsuyoshi Kobashigawa<sup>1</sup>, Hisae Ichida<sup>1</sup>, Yasuhiro Katsumata<sup>1</sup>, Yasushi Kawaguchi<sup>1</sup>, Hisashi Yamanaka<sup>1</sup>

<sup>1</sup>Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, <sup>2</sup>Department of Respiratory Medicine, National Hospital Organization Himeji Medical Center, Hyogo, Japan

Conflict of interest: None

[Introduction] Hypocomplementemic urticarial vasculitis is classified Small Vessel vasculitis, called anti-C1q Vasculitis. This disease is rare, occasionally complicated with SLE. Anti-C1q antibodies were reported to be significance of etiology of HUVS and SLE, We reported Anti-C1q antibodies is associated with SLE. [Case1] A woman had edematous erythema, was diagnosed with Urticarial vasculitis. She had urinary protein, serum ANA, anti-ds DNA antibody, hypocomplementemia, lupus nephritis type II. She was diagnosed SLE with HUVS. Low dose steroids ameliorated her urinary protein, but Urticarial vasculitis is incurable, the levels of Anti-C1q antibodies increase. High dose steroids, tacrolimus and intravenous cyclophosphamide ameliorated her urticarial vasculitis. The levels of anti-C1q antibodies decreases. [Case2] A woman had erythema urticatum, urinary protein, hypocomplementemia, serum ANA. She had leukocytopenia, anti-ds DNA antibodies, lupus nephritis, urticarial vasculitis. She diagnosed SLE with HUVS. High dose steroids ameliorated her symptoms and urticarial vasculitis. Anti-C1q antibodies titer decrease. [Clinical Significant] In a SLE with HUVS, the levels of anti-C1q antibodies fluctuated along with disease activity. It is conceivable that this lesion support significant of etiology.

### P1-155

#### Urine protein-to-creatinine ratio in an untimed urine collection is a reliable measure of proteinuria in Japanese patients with lupus nephritis

Hirokazu Nishina, Yasuhiro Katsumata, Masanori Hanaoka, Yuko Okamoto, Hisae Ichida, Yasushi Kawaguchi, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Objectives] According to Japanese Society of Nephrology guideline, 24-hour urinary protein is a standard way to check the proteinuria. According to ACR, it is recommended that we check the protein-to-creatinine ratio (P/C) when it is difficult to collect urine for a day. In an overseas report, the reliability in the lupus nephritis patient is controversial. But there are few report in Japanese. As the evaluation method of renal function, eGFR is recommended. But there are few reports on the reliability of patient of lupus nephritis. In this study, it was aimed to verify the reliability of P/C and other allied inspection in lupus nephritis patient. [Methods] Japanese lupus nephritis patients who admitted to our hospital from April 2010 to September 2014 were included. We collected data from the medical records, and was statistically analyzed it. [Results] P/C of spot urine and 24-hour urinary protein were correlated (n=23, pearson's  $\rho=0.80$ ). P/C of 24-hour urine and 24-hour urinary protein were correlated (n=32, pearson's  $\rho=0.87$ ). CCr (24-hour urine) and eGFR were correlated (n=38,  $\rho=0.68$ ). [Conclusion] Tests such as P/C of spot urine and eGFR are correlated with the conventional tests in Japanese lupus nephritis patients. And considered to be an alternative to conventional tests.

### P1-156

#### The clinical characteristics and the profile of autoantibodies in lupus mesenteric vasculitis(LMV)

Kazuyoshi Kubo, Kunihiko Umekita, Ayako Kawano, Yumi Kariya, Yayoi Hashiba, Motohiro Matsuda, Katoko Takajo, Shunichi Miyauchi, Norio Kusumoto, Ichiro Takajo, Yasuhiro Nagatomo, Akihiko Okayama

Department of Rheumatology, Infectious Diseases and Laboratory Medicine, Faculty of Medicine, University of Miyazaki

Conflict of interest: None

[OBJECTIVE] To evaluate the clinical characteristics of lupus mesenteric vasculitis (LMV) and the profile of autoantibodies in LMV. [METHODS] A retrospective cohort study was performed among patients admitted to our department between April 2008 and September 2014. The diagnosis of LMV based on clinical symptoms and imaging characteristics like abdominal CT scan. We reviewed the laboratory findings and complication associated with systemic lupus erythematosus (SLE). To evaluate the autoantibody profile in LMV, sex-age matched 10 patients with lupus nephritis (LN) were enrolled as control. [RESULTS] Out of 78 patients with SLE, five patients were diagnosed with LMV. In the clinical finding characteristics of LMV patients, the values of SLE-DAI, serum albumin, creatinine kinase, C3, and CRP were 23, 2.6 g/dl, 0.55 mg/dl, 47 mg/dl, and 5.22 mg/dl, respectively. The positive rate of anti-Sm antibody and anti-RNP antibody was higher in patients with LMV than in patients with LN (80% v.s 40% and 60% v.s 20%, respectively). During an observational period of this study, 60% of patients with LMV developed neuropsychiatric SLE. [CONCLUSION] Our findings suggested that there are some differences in the profile of autoantibodies and complication associated with SLE between LMV and LN.

### P1-157

#### The outcomes of pregnancy in patients with systemic lupus erythematosus

Mei Tani, Yoshiyuki Arinuma, Tatsuo Nagai, Kako Kodama, Yu Matsueda, Nobuhiro Sho, Eisuke Ogawa, Tatsuhiko Wada, Sumiaki Tanaka, Shunsei Hirohata

Department of Rheumatology and Infectious Diseases Kitasato University School of Medicine, Kanagawa, Japan

Conflict of interest: None

[Objectives] The present study was undertaken to evaluate pregnancy and fetal outcomes in patients with systemic lupus erythematosus (SLE). [Methods] We experienced 52 cases of pregnancy in 41 SLE patients from 2009 to 2014. Of 52 cases, analyses were restricted to 48 cases of pregnancy in 38 patients who had been visiting obstetricians of our hos-

pital regularly. [Results] Of 48 cases, 22 resulted in full term birth (45.8%), 9 in preterm birth (18.8%), 6 in spontaneous abortion or stillbirth (12.5%), 6 in elective termination of pregnancy (12.5%), and 5 were still pregnant (10.4%). Although the dose of prednisolone was increased due to lupus flares during pregnancy in six cases, 1 ended in full term birth, 2 in preterm birth, 1 in stillbirth and 2 in elective termination of pregnancy. The risk of spontaneous abortion and stillbirth had no association with anti-DNA antibodies, anti-Sm antibodies or antiphospholipid syndrome. Two cases of neonatal lupus erythematosus were born to one patient with anti-SSA/Ro antibodies. One neonate complicated ventricular septal defect, where maternal anti-SSA/Ro antibodies were negative. [Conclusion] The outcomes of pregnancy in SLE patients might be relatively satisfactory in spite of some cases with lupus flares during pregnancy.

### P1-158

#### Clinical picture and outcome of newly diagnosed lupus nephritis during the last decade

Hidetoshi Kagawa<sup>1</sup>, Tsutomu Hiromasa<sup>1</sup>, Ryutaro Yamanaka<sup>1</sup>, Reika Takemoto<sup>1</sup>, Ken-ei Sada<sup>2</sup>, Hirofumi Makino<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Himeji Red Cross Hospital, Himeji, Japan, <sup>2</sup>Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

Conflict of interest: None

[Objectives] Because the Himeji Red Cross Hospital is the only specialized facility for managing lupus nephritis (LN) in our medical area, our data on LN incidence, clinical picture and outcome may provide an overall picture of systemic lupus erythematosus (SLE) and LN. [Methods] We investigated 120 patients newly diagnosed with SLE between 2005 and 2013 in our hospital and assessed their outcomes in October 2014. [Results] Forty-seven (39%) of the 120 SLE patients had LN, which was diagnosed at the onset of SLE in 43 cases (91%). Hypocomplementemia (83%) and anti-double-strand DNA antibody positivity (89%) occurred more frequently in those with LN than in those without it. Renal biopsy was performed in 31 patients (66%), revealing class II disease in 6.5%, class III in 38.7%, class IV in 22.6%, class V in 22.6%, and class V+III/IV in 9.7%. Forty-one patients (87%) were treated with corticosteroids and immunosuppressive drug, whereas six (13%) received corticosteroids alone. Complete remission was achieved in 87%. Three elderly patients (9.6%) died of sepsis, pneumonia and lung cancer, respectively. No patient developed terminal renal failure. [Conclusion] Our data suggest a decreasing trend in incidence and mortality from LN.

### P1-159

#### Clinical examination of pericardial effusion in patients with systemic lupus erythematosus

Kazuko Suzuki, Hiroko Sato, Kazunobu Ichikawa, Tsuneo Konta, Isao Kubota

Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, Yamagata, Japan

Conflict of interest: None

[Objectives] Although cardiac manifestation is relatively rare in SLE patients in Japan, we often encounter asymptomatic pericardial effusion (PE) implying the potential cardiac involvement. To examine the relationship between PE and the clinical parameters, we conducted a cross-sectional study in SLE patients who were admitted to our hospital. [Methods] The study subjects were 22 SLE patients (4 males, 18 women, average 39 years of old) without apparent heart disease, other collagen diseases, and serious systemic disease, who underwent cardiac ultrasound. [Results] Although left ventricular ejection fraction (EF) was  $\geq 60\%$  and cardiac function was maintained in all cases, PE was observed in 6 cases (27.3%). Compared with the PE-negative group, the PE-positive group showed a significantly higher BNP levels ( $P = 0.008$ ). However, other parameters including EF, left atrium diameter, left ventricular end-diastolic diameter, inferior vena cava diameter, h-FABP, CH50, anti-ds-DNA antibody and CRP were not significantly different between them. In the ROC analysis, the cut-off value of BNP to predict PE was

41.3 pg/ml (100% sensitivity, specificity 75%). [Conclusion] The elevation in serum BNP levels might predict asymptomatic PE in SLE patients.

### P1-160

#### Predictors of therapeutic outcomes in patients with neuropsychiatric systemic lupus erythematosus

Kunihiro Ichinose<sup>1</sup>, Kazuhiko Arima<sup>2</sup>, Masataka Umeda<sup>1</sup>, Shoichi Fukui<sup>1</sup>, Ayako Nishino<sup>1</sup>, Yoshikazu Nakashima<sup>1</sup>, Takahisa Suzuki<sup>1</sup>, Yoshiro Horai<sup>1</sup>, Tomohiro Koga<sup>1</sup>, Shin-ya Kawashiri<sup>2</sup>, Naoki Iwamoto<sup>1</sup>, Yasuko Hirai<sup>1</sup>, Mami Tamai<sup>1</sup>, Hideki Nakamura<sup>1</sup>, Tomoki Origuchi<sup>3</sup>, Atsushi Kawakami<sup>1</sup>

<sup>1</sup>Departments of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, <sup>2</sup>Departments of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, <sup>3</sup>Rehabilitation Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Conflict of interest: None

[Objectives] Neuropsychiatric systemic lupus erythematosus (NPSLE) is a serious organ disorder with a variety of symptoms. Our purpose is to understand the immunopathogenic and clinical aspects of NPSLE. [Methods] We analyzed the laboratory data, symptoms and therapeutic outcomes 1 year after treatment, and the prognostic factors of 28 NPSLE patients and 27 cytokine profiles in pretreatment samples of their cerebrospinal fluid (CSF). [Results] Twelve patients were responders at 1 year post-treatment; their median age at NPSLE onset was 29 years versus 39 years in the non-responders. The median duration from SLE onset of NPSLE was 1.5 years in responder versus 11 years in non-responder. The CSF interleukin (IL)-10, interferon (IFN)- $\gamma$  and tumor necrosis factor (TNF)- $\alpha$  levels before the treatment were significantly higher in the non-responders. Ranking of the cytokines to distinguish responder from non-responder by weighted-voting algorithm showed that the combination of IL-10, TNF- $\alpha$ , IL-6, IFN- $\gamma$ , IL-4 and IL-13 had a highest Matthews correlation coefficient. [Conclusion] Younger and shorter disease duration of NPSLE patients had significantly better therapeutic outcomes. Measurement of multiple cytokines in pretreatment could distinguish responder from non-responder patients.

### P1-161

#### A case report of systemic lupus erythematosus combined with Castleman's disease

Atsushi Omoto, Aki Sakashita, Akiko Ido, Masatoshi Kadoya, Wataru Fukuda

Center for Rheumatic Disease, Japan Red Cross Kyoto Daiichi Hospital, Kyoto, Japan

Conflict of interest: None

A 49-year old male complained of fever and watery diarrhea, which was diagnosed as ischemic colitis in May 2014. Blood examination showed hemolytic anemia, low complement (C3 16mg/dl), and high titer of anti-nuclear antibody (5120x, homogenous pattern). He was admitted to this hospital for further examination in August 2014. Based on the data of ds-DNA antibody, proteinuria, the patient was diagnosed as in active phase of SLE. Whole body CT scan showed diffuse lymphadenopathy and the subclavicular lymph node was removed and the histological examination was compatible with Castleman's Disease. The patient was treated with prednisolone 40mg/day and received a marked decrease in size of the swelled lymph nodes and anemia was remarkably improved. Castleman's disease is a rare lymphoproliferative neoplasm that has features overlapping various autoimmune disease including SLE. This disorder should be considered in autoimmune diseases with unremitting or progressive adenopathy.

### P1-162

#### Acute onset systemic lupus erythematosus male patient with Libman-Sacks endocarditis and Bickerstaff brainstem encephalitis

Seiichiro Ando, Takayuki Kon, Kazuhisa Nozawa, Ken Yamaji, Naoto Tamura, Yoshinari Takasaki

Department of Rheumatology and Internal Medicine, Juntendo University

Conflict of interest: None

[A case] 39-year-old Japanese man. He had exertional dyspnea from August 2013, and was taken to hospital unconscious 26<sup>th</sup> September. Because of Aortic regurgitation, fever, and inflammation, he was diagnosed as infective endocarditis and autoimmune hemolytic anemia. High dose glucocorticoid was not effective. He was referred to our hospital and diagnosed as systemic lupus erythematosus (SLE) by anti-nuclear antibody, anti-DNA antibody, urinary sediment, hemolytic anemia. Although glucocorticoid pulse therapy and high dose glucocorticoid were performed at first, they were not effective to fever and consciousness disorder. According to cerebrospinal fluid and Brain MRI, CNS lupus and cerebral embolism were ruled out. From multiple motor neuropathy with impairment of consciousness and anti-GQ1b antibody positive, this case was diagnosed as Bickerstaff brainstem encephalitis. A combination treatment with glucocorticoid and single filtration plasmapheresis was improved various clinical conditions. Valvular disease was considered Libman-Sacks endocarditis because of refractory to antibiotics and blood culture negative. [The clinical significance] Acute onset SLE with Libman-Sacks type endocarditis and Bickerstaff type brainstem encephalitis is rare case.

### P1-163

#### A role of antiphospholipid antibody for determination of manifestations in systemic lupus erythematosus

Yusuke Yamada<sup>1</sup>, Kazuhisa Nozawa<sup>1</sup>, Hirofumi Amano<sup>1</sup>, Iwao Sekigawa<sup>2</sup>, Yoshinari Takasaki<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine, Tokyo, Japan, <sup>2</sup>Department of Internal Medicine and Rheumatology, Juntendo University Urayasu Hospital, Chiba, Japan

Conflict of interest: None

[Objectives] Antiphospholipid syndrome (APS), which is known to induce thrombosis and recurrent fetal loss, can be classified into primary APS and secondary APS. Systemic lupus erythematosus (SLE) consists of heterogeneous patient's population with different clinical manifestations. Therefore we undertook this research project to clarify antiphospholipid antibody (APL) contribution for the clinical manifestations. [Methods] SLE patients with APL (n=47) were enrolled from database of SLE patients in Juntendo University Database of Erythematosus (JUDE). Their clinical manifestations were compared to those in SLE patients without APL (n=47). [Results][Conclusion] SLE patients having APL showed higher prevalence in CNS involvement, skin lesion (erythema), hypocomplementemia, and elevation of anti-DNA antibody in serum. Furthermore, we divided SLE patients having APL into three groups characterized as thrombosis (+), recurrent fetal loss (+), and no events of these manifestations. The APL positive SLE patients with thrombosis showed higher prevalence in overlapping with Sjogren syndrome, thrombocytopenia, and hyperlipidemia compared to the APL positive SLE patients without the events. Moreover, the APL positive SLE patients with recurrent fetal loss showed higher prevalence in thrombosis.

### P1-165

#### Safety and effectiveness of Tacrolimus Treatment during Pregnancy in Systemic Lupus Erythematosus

Yuri Hiramatsu, Shuzo Yoshida, Yuko Kimura, Tooru Takeuchi, Shigeaki Makino, Toshiaki Hanafusa

Department of Internal Medicine (I), Osaka Medical College, Osaka, Japan

Conflict of interest: None

[Objectives] Pregnancy with systemic lupus erythematosus (SLE) is associated with an increase risk of adverse maternal and fetal outcomes. Lupus activity in pregnancy is mainly controlled with prednisone and immunosuppressant including tacrolimus (Tac) for severe lupus in pregnancy are limited. [Methods] We report four SLE patients treated with Tac during pregnancy. SLE flares were determined by the Lupus Activity Index-Pregnancy (LAI-P) score. We also measured Tac blood concentration in a gestational period. [Results] The mean patient age, the mean dose of

prednisolone (PSL), the mean dose of Tac, was 31.5 years, 10.3 mg/day, and 2 mg/day, respectively. The average of delivery weeks was 35.5 weeks (31-38w) and the mean child born weight was 2453 g (1512-3030 g). Because one case accepted lupus nephritis aggravation all over the pregnancy progress, we had to start treatment with Tac. In all cases, the mother's Tac blood concentration in a gestational period after the second pregnancy trimester was a low value slightly in comparison with non-pregnant time. No teratogenic effects of Tac were observed in our study. [Conclusion] In this study, there were no obvious side effects of Tac during pregnancy.

### P1-166

#### Clinical characteristics of ANCA-positive SLE patients

Kenichi Ueno, Dai Kishida, Yasuhiro Shimojima, Wataru Ishii, Shuichi Ikeda

Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Nagano, Japan

Conflict of interest: None

**Objectives:** Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of multiple autoantibodies, and some SLE patients are ANCA-positive. In this study, we sought to clarify clinical characteristics of ANCA-positive SLE patients. **Methods:** We retrospectively reviewed clinical records in ANCA-positive SLE patients who were admitted to our hospital from April 2010 to October 2014. **Result:** Five SLE patients were ANCA-positive (1 male and 4 females). Two of them were positive for MPO-ANCA and the other 3 patients were positive for PR3-ANCA. Four patients had neuropsychiatric manifestations, 3 patients had renal involvement, and 2 patients had interstitial pneumonia. The renal biopsy showed no vasculitic lesions. All patients were treated with prednisolone, and intravenous cyclophosphamide pulse or tacrolimus were added in 3 patients with renal involvement. **Conclusion:** ANCA-positive SLE patients tended to show multiorgan involvements, and need a combination therapy with steroid and immunosuppressant.

### P1-167

#### Association study of Glutamate-cystein ligase (GCL) polymorphisms with susceptibility to systemic sclerosis (SSc)

Akiko Tochimoto, Yasushi Kawaguchi, Kae Takagi, Manabu Kawamoto, Tomoaki Higuchi, Chikako Fukasawa, Hisae Ichida, Yasuhiro Katsumata, Takahisa Gono, Masanori Hanaoka, Yuko Okamoto, Hidenaga Kawasumi, Mari Tochihiro, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Objectives] Systemic sclerosis (SSc) is characterized by fibrosis of skin and internal organs and microvascular injury. Endothelial injury may be induced by the actions of free radicals or environmental factors with immune activation. Glutathione (GSH) is an important antioxidant. It has been reported that GSH concentration is decreased in the SSc fibroblast. Nakamura et al reported that GCL modifier subunit (*GCLM*) polymorphism was associated with myocardial infarction. In this study, we examined whether polymorphisms of the GCL gene are associated with susceptibility to SSc. [Methods] We investigated 235 SSc patients and 346 healthy controls. Gene polymorphisms of *GCLM* rs41303970 and GCL catalytic subunit (*GCLC*) rs17883901 were determined using TaqMan SNP genotyping assay. [Results] There was no association between GCL polymorphisms and SSc. However, the frequency of *GCLM* rs41303970 T allele was tend to be higher in diffuse cutaneous SSc than healthy controls (P=0.053) and significantly higher than limited cutaneous SSc (P=0.02). [Conclusion] Our results suggest *GCLM* polymorphism may be associated with the severity of skin fibrosis when SSc developed.

### P1-168

#### Involvement of $\gamma$ AT cells in the pathogenesis of bleomycin-induced pulmonary fibrosis

Seiji Segawa, Daisuke Goto, Akira Iizuka, Isao Matsumoto, Takayuki

Sumida  
Department of Internal Medicine, Faculty of Medicine, University of  
Tsukuba

Conflict of interest: None

[Objectives] Interstitial pneumonia (IP) is one of the critical complications in patients with several autoimmune diseases. However, the exact mechanism of IP remains elusive. The purpose of this study is to clarify the role of  $\gamma\Delta T$  cells in bleomycin-induced IP murine models. [Methods] 1. C57BL/6 (WT) and TCR $\Delta$  deficient (TCR $\Delta^{-/-}$ ) mice were treated with bleomycin. At 21 days after bleomycin exposure, the pathology and collagen production in lungs were examined. 2.  $\gamma\Delta T$  cells in naive pulmonary lymphocytes from WT mice were analyzed by flow cytometry (FCM). 3. At 3, 7, 14, 21 days after bleomycin exposure, the number of pulmonary  $\gamma\Delta T$  cell subsets was analyzed by FCM. [Results] 1. TCR $\Delta^{-/-}$  mice showed pronounced hypercellularity and intimal thickening in lung parenchyma, and overproduction of collagen in lungs compared with WT mice. 2. Pulmonary  $\gamma\Delta T$  cells were separated into  $\gamma\Delta T1$  (NK1.1<sup>+</sup>  $\gamma\Delta TCR^{lo}$ ),  $\gamma\Delta T1/17$  (NK1.1<sup>-</sup>  $\gamma\Delta TCR^{lo}$ ) and  $\gamma\Delta T17$  (NK1.1<sup>-</sup>  $\gamma\Delta TCR^{hi}$ ) cells. 3. After bleomycin exposure, the number of pulmonary  $\gamma\Delta T1$  cells increased at day 3 and day 7, whereas  $\gamma\Delta T1/17$  and  $\gamma\Delta T17$  cells increased at day 7. [Conclusion] Pulmonary  $\gamma\Delta T$  cell subsets might play a crucial role in the development of IP.

### P1-169

#### Clinical features of limited cutaneous systemic sclerosis with anti-centromere antibody

Taro Horino, Tatsuki Matsumoto, Kazu Ode, Koji Ogata, Yoshiko Shimamura, Kosuke Inoue, Yoshinori Taniguchi, Yoshio Terada  
Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi University

Conflict of interest: None

[Objectives] The clinical features of limited cutaneous systemic sclerosis (lcSSc) with anti-centromere antibody remain unclear. Our goal was to study the prevalence of organ damages of lcSSc with anti-centromere antibody. [Methods] 30 patients who had hospitalized in our outpatient clinic from 2012 to 2014 were enrolled. We assess the correlation between the clinical characteristics and data. [Results] Female were 28 (93.3%). Mean age was 68.8 years old. The duration between onset of Raynaud phenomenon and first visit was 12.1 year. Incidence of Raynaud phenomenon and sclerodactylia were 90.0 and 100.0%. PBC, Hashimoto's disease, Sjogren syndrome, pulmonary hypertension, interstitial pneumonia, renal dysfunction were 36.6, 20.0, 16.6, 16.6, and 6.6%, respectively. BNP was 73.02±29.6 pg/ml, KL-6 was 222.6±18.2 U/ml, Cr was 0.67±0.03 mg/dl, BUN was 15.2±0.5 mg/dl, UA was 4.68±0.24 mg/dl, CRP was 0.36±0.16 mg/dl, and eGFR was 70.8±2.6 ml/min/1.73m<sup>2</sup>. BNP as a biomarker for pulmonary hypertension had positive correlation to KL-6 and LDH for interstitial pneumonia, and negative correlation to Alb and t-Cho. [Conclusion] The results of our study suggested that the prognosis of pulmonary hypertension could be associated with the prognosis of interstitial pneumonia and malabsorption.

### P1-170

#### Can we predict the exist of pulmonary artery hypertension associated with connective tissue diseases (APAH) using Nailfold capillaroscopy (NFC)?

Yumiko Nobuhara, Yoshikazu Fujikawa, Yuzuru Yamamoto, Takashi Nakazawa  
Osaka Saiseikai Nakatsu Hospital

Conflict of interest: None

OBJECTIVES: NFC is useful tool in patients with systemic sclerosis (SSc) and the reduced nailfold capillary density was reported to be associated with APAH. We aimed to examine whether 'capillary loss'(CL) or 'ramified capillary'(RC) at NFC is predictive factor for APAH in connective tissue disease (CTD) patients. METHODS: 12 patients (2 of diffuse, 7 of limited SSc, one of mixed CTD and one of SLE), performed right heart catheterization and NFC from May 2013 to October 2014, were in-

cluded. We analyzed the relation between NFC findings and APAH, respectively. We performed NFC with digital microscope (Dino-Lite Pro®), and we evaluated the findings with the standard proposed by M. Cutolo (Ann Rheum Dis 2012;71). RESULTS: In 10 of 11 patients diagnosed as APAH. CL and RC findings were found in 7 of them. 2 of them demonstrated only enlarged capillaries, one has treated with PDE5 inhibitor for 2 years, another has complicated pneumoconiosis. One SLE-APAH case showed only non specific change. Non-APAH case with MCTD also showed non-specific change. One case with CL and RC findings developed APAH in 1 year. CONCLUSIONS: Many of SSc-APAH cases showed CL and RC findings. We need to evaluate more cases and longer follow-up.

### P1-171

#### Consider systemic sclerosis(SSc) patients in our hospital by dermoscopy

Tetsuya Furukawa, Takeo Abe, Yuichi Yokoyama, Momo Maruoka, Takahiro Yoshikawa, Takuya Hino, Atsushi Saito, Aki Nishioka, Masahiro Sekiguchi, Naoto Azuma, Masayasu Kitano, Shinichiro Tsunoda, Kiyoshi Matsui, Hajime Sano  
Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine

Conflict of interest: None

[Objectives] In recent years, nailfold capillary is drawing attention from Systemic sclerosis diagnosis, it was also used in the new SSc classification criteria proposed by the ACR/EULAR 2013. Moreover, it seems that dermoscopy is useful to early diagnosis and treatment VEDOSS (Very early diagnosis of Systemic Sclerosis), detailed consideration by nailfold capillary in Japan have not been made. [Methods] We examined outpatients diagnosed with SSc by dermoscopy (DermLite III J.Hewitt) to August to October 2014 in our hospital. The number of patients were 83 people (12 men and 73 women). The average age was 63.3 ± 12.2 yr. The average Raynaud's phenomenon onset as the duration of the illness was 10.4 ± 9.7 yr. [Results] No specific alteration was 5 people (average age: 64.0 ± 9.6 yr, disease duration: 3.0 ± 6.7yr), early pattern was 29 people (59.7 ± 13.6 yr, 7.3 ± 8.6 yr), active pattern was 30 people (65.3 ± 11.8yr, 11.1 ± 9.1 yr) and late pattern was 19 people (65.4 ± 10.6 yr, 16.1 ± 10.1 yr). [Conclusion] Disease duration was parallel in proportion to exacerbation peripheral vascular findings. We consider in detail including the drug dosing contents such as steroids, immunosuppressants and vasodilators announce addition of literature.

### P1-172

#### Viral infection (reactivation) sometimes exacerbate disease activity of CTD

Kazuhiro Hatta, Ai Yaku, Shuko Hashimoto, Teruhisa Azuma, Hiroyasu Ishimaru  
Department of General Internal Medicine, Tenri Hospital, Tenri, Japan

Conflict of interest: None

[Objectives] MCTD, which is representative disease of AntiU1-RNP Ab positive disease, sometime showed intermittent and recurrent attacks of fever and arthralgia. The pathogenesis seemingly is due to some external factor like drugs or virus infection. The similar condition were those of severe drug eruption (DIES), caused by viral reactivation induced by some specific drugs. [Methods] Investigation of series of cases, which seemed exacerbate by CMV infection or reactivations. [Results] We experienced the carried-over case of 18 year-old MCTD with PAH female patient who recurred intermittently MCTD flairs-up almost everytime with CMV-IgM elevation. [Conclusion] We saw several more cases of sjogren syndrome, EGPA and DIES of CTD patients, and reached to the conclusion that virus infection like CMV might sometime induce the flare up of the collagen diseases.



### P1-173

#### Retrospective Analysis of Patients with Systemic Sclerosis-Related Interstitial Lung Disease (SSc-ILD) Treated by Intermittent Intravenous Cyclophosphamide (IVCY)

Yoshihiro Yoshida, Kazuhiro Yokota, Haruhiko Akiba, Hiroshi Kajiyama, Kojiro Sato, Yuji Akiyama, Toshihide Mimura  
Department of Rheumatology and Applied Immunology, Saitama Medical University Faculty of Medicine, Saitama, Japan

Conflict of interest: None

[Objectives] The previous studies have shown that IVCY is effective on SSc-ILD. We retrospectively analyzed our SSc-ILD cases treated by IVCY to evaluate the clinical efficacy and safety for Japanese patients. [Methods] From January 2006 until September 2014, 16 progressive SSc-ILD patients received the treatment at our department. We compared CT images, pulmonary function tests (PFT), 6-minute walk tests (6MWT), and serum KL-6 levels before and after IVCY in these patients. The dose of IVCY administered to the patients was 500 mg every four weeks for 6 months. [Results] The patients (5 males and 11 females) were 57.4 years old on average. Eventually, 14 patients completed the six-time administrations. The average dosage was 495 mg/month. Two patients withdrew because of an infectious disease, and one died from pulmonary hypertension after the sixth IVCY. Thoracic CT reveals pulmonary conditions improved in five patients, unchanged in eight patients and worse in one. Furthermore, no significant differences were found in the results of PFT and 6MWT, however, KL-6 levels significantly decreased from 1548 to 953. [Conclusion] Our results suggest that IVCY at doses of 500 mg/month is effective on Japanese patients with progressive SSc-ILD.

### P1-175

#### Clinical features of dermatomyositis patients associated with pruritic papules

Naomi Yoshida, Shinjiro Kaieda, Masaki Okamoto, Morihiro Tajiri, Yukiko Kunitake, Daisuke Wakasugi, Masaki Tominaga, Hiroaki Ida  
Division of Respiratory, Neurology and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Fukuoka, Japan

Conflict of interest: None

(Objective) Clinical features including skin involvement is still important to predict the disease prognosis. We had 3 DM patients, who were killed by rapid progressive-interstitial lung disease (ILD). Pruritic papules over the trunk, neck and extensor sides of extremities were observed in all dead patients. We sought to analyze the correlation between pruritic papules and disease severity in DM patients associated with ILD. (Methods) We classified 3 groups of 16 DM patients as follows: Group A) pruritic papules were observed. B) pruritus was present whereas pruritic papules were not observed. C) pruritus was absent. We examined the serum levels of IL-6, CRP, ferritin, CPK and KL-6 before the immunosuppressive therapy initiation. Respiratory function test was performed. (Results) IL-6 was significantly elevated in patients with pruritic papules (group A) than that seen in other groups (group B and C). CRP was also increased. In respiratory function test, there is no significant difference among 3 groups. All DM patients who developed pruritic papules became feverish. (Conclusion) The presence of pruritic papules in DM patients was associated with systemic inflammatory response; however, it did not correlate with the severity in the lung involvement.

### P1-176

#### The prognostic factors in Polymyositis and Dermatomyositis

Rintaro Saito, Kenta Misaki, Yuri Nakamura, Yoshie Gon, Takumi Nagamoto, Hisayo Horiuchi, Hirota Yamada, Toshihiko Yokota  
Department of Endocrinology and Rheumatology, Kurashiki Central Hospital, Okayama, Japan

Conflict of interest: None

Objectives We examined prognostic factors of PM/DM in our hospital. Methods We extracted the patients diagnosed with PM/DM based on

the criteria of Bohan & Peter from January, 2002 until September, 2014 in our hospital. We examined about the onset age, serum CK, ferritin level (peak), anti-Jo-1 antibody, malignancy, interstitial pneumonia (IP), dysphagia and treatment. Results 28 cases (PM13 cases, DM15 cases) were enrolled, and the onset was 62.9±11.4 years old (female: 19 (68%), male: 9 (32%)), PM/DM with IP: 17 (61%), with malignancy: 17 (61%), with dysphagia: 5 (18%). Serum anti-Jo-1 antibody was positive in only 2 cases (7%). The peak serum CK level was 4441.6±1024.6 IU/L, and ferritin was 896.3±406.9 ng/ml. 12 cases (43%) needed to treat with steroid pulse therapy, 9 cases (35%) were administered only steroid therapy, and 17 cases were steroid with other immunosuppressive agents (one agent: 9 (35%), over two agents: 8 (31%)). 16 cases (57%) survived and 12 (43%) died. In comparison in survival group (L) and the death group (D), L group was significantly high in the serum ferritin level (L: 191.5 ±71.3 ng/ml vs D: 1865.5 ±765.5 ng/ml); (p=0.02)). Conclusion We confirmed that serum ferritin level, complication of malignancy and IP, and dysphagia were contributed to the prognosis in PM/DM.

### P1-177

#### Longterm outcome of interstitial lung disease in inflammatory myopathy

Machiko Mizushima, Hidehiro Yamada, Yoshioki Yamasaki, Seido Ooka, Masaomi Yamasaki, Takahiro Okazaki, Shoichi Ozaki  
Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna University, School of Medicine, Kawasaki City, Japan

Conflict of interest: None

[Objectives] The aim of this study was to assess the long term clinical course and outcome of interstitial lung disease (ILD) in idiopathic inflammatory myopathy (IIM) and to determine predictive factors for the outcome of IIM-associated ILD. [Methods] Among 228 patients with IIM, 140 patients with ILD were identified by medical records search at our hospital from 1984 to 2010. Pulmonary high-resolution computed tomography (HRCT) scan was available in 93 patients and their clinical features were analyzed. [Results] Mean follow up period (SD) of the 93 patients was 69 (54) months. Clinical ILD was deteriorated in 22 patients, while ILD was stabilized during the period, in 71 patients. Univariate analysis indicated exertional dyspnea (p=0.0453), cough (p=0.0216), Gottron's sign (p=0.0021), higher values of aspartate transaminase (AST) (p=0.0034) were associated with ILD deterioration. 7 patients were died for respiratory failure within 1 year, they were all DM patients, and had periungual erythema. [Conclusion] Our study suggested that respiratory symptom and dermal findings were important predictive factors of ILD deterioration.

### P1-178

#### Clinical investigation regarding anti-melanoma differentiation-associated gene 5 antibody in dermatomyositis patients with interstitial lung disease

Daisuke Hirano, Jo Nishino, Soichi Yamada, Konomi Ashihara, Akiko Yoshida, Satoru Onoda, Kenichi Kato, Shusaku Fukaya, Shunji Yoshida  
Division of Rheumatology and Infectious Diseases, Department of Internal Medicine, Fujita Health University School of Medicine, Japan

Conflict of interest: None

Objective: Anti-melanoma differentiation-associated gene 5 (MDA5) antibodies are predominantly positive in patients with clinically amyopathic dermatomyositis (CADM), which is often associated with rapidly progressive interstitial lung disease (RP-ILD). The present study aimed to investigate the clinical significance of anti-MDA5 antibodies in DM patients with ILD. Methods: The clinical characteristics of 13 DM patients with ILD (6 men and 7 women) whose anti-MDA5 antibody levels were measured from 2011 to 2014 were investigated. They were based on retrospective examination of their medical records. Results: Patient mean age was 55.1±16.8 years. A total of 4 patients had DM and 9 had CADM. Anti-MDA5 antibodies were positive in 8 of the 13 patients (61.5%). Of these, 5 patients had associated RP-ILD (62.5%) and 4 died during the study period. Conversely, 2 of the 5 anti-MDA5 antibody-negative patients had associated RP-ILD (40%) and 1 died during the study period. The mortality rate was significantly higher in anti-MDA5 antibody-posit-

tive patients with high ferritin levels ( $\geq 1000$  ng/ml). Discussion and Conclusion: The present findings suggest that anti-MDA5 antibody positivity with high ferritin levels is a poor prognostic factor for DM patients with ILD.

### P1-179

#### Comparison examination about the difference of the result of the insurance adaptation anti-ARS antibody and of Euroline Myositis profile 3, in polymyositis, dermatomyositis, and interstitial pneumonia

Hidekazu Futami, Takuya Nakazawa, Ryutarō Matsumura  
Center of Rheumatology, Allergy and Clinical Immunology, National Hospital Organization Chiba East National Hospital

Conflict of interest: None

[Objectives] To compare the result of the insurance adaptation anti-ARS antibody and of Euroline Myositis profile 3, in polymyositis, dermatomyositis, and interstitial pneumonia. [Methods] Comparison examination about the result between 23 cases, which measured both the insurance adaptation anti-ARS antibody and Euroline Myositis profile 3 in our department, was carried out. [Results] 7 are positive of the insurance adaptation anti-ARS antibody, and all the cases are diagnosed as polymyositis or dermatomyositis. Those all were positive in Euroline, 4 of Jo-1, 1 of PL-7, 1 of EJ, 1 of SRP, 6 of Ro-52. 16 are negative of the insurance adaptation anti-ARS antibody, and 5 were positive in Euroline. Takayasu arteritis, polymyositis + interstitial pneumonia, dermatomyositis, Sjogren-syndrome + interstitial pneumonia, idiopathic interstitial pneumonia were contained. [Conclusion] It seems that an insurance adaptation anti-ARS antibody is useful to detection of polymyositis and dermatomyositis. Moreover, Euroline also may be useful to consider the relation with other rheumatic diseases.

### P1-180

#### A case of Measurement of anti-ARS-Antibody was useful for therapy

Takahiro Onishi<sup>1</sup>, Kusuki Nishioka<sup>2</sup>

<sup>1</sup>Ise Red Cross Hospital Department Of Rheumatology, <sup>2</sup>Tokyo Medical University Institute of Medical Science

Conflict of interest: None

We report a case this time we from symptoms diagnosis was difficult but the anti ARS antibody measurement is useful. Patients with 72-year-old had a history of men sleep apnea, diabetes is. This time three months earlier than emerge from both shoulders and hand pain, leg pain, had worsened during the night. Than about 1 month ago my hands swell bending difficult to become. 38 ° c after that tremor accompanied by fever appeared on the increased leg pain and was admitted. Come Academy at oral ulceration is also without rash, admitted with severe edema of both arms and legs. No joint pain, both on the acknowledged the pain in lower limbs. Of fibromyalgia tender points are were in the negative. treatment at PSL20mg per day. At a later date and turned out anti ARS antibody 31.3 Yang. Improve symptoms of fever or pain no. 15 disease, the patient was discharged. However appeared 1 week later than nails surrounding Erythema, mechanic's hand was seen. Hard skin collagen hyperplasia and markedly in skin biopsy, in Scleroderma using our findings. Closings anti ARS antibody is Myositis detected before or between developing pneumonia and the present case lacks muscle symptoms between was effective in thinking about treatment and because no Interstitial pneumonia is turned out early.

### P1-181

#### A case of anti-SRP positive polymyositis initially diagnosed as Sjogren's syndrome

Takayoshi Kurabayashi, Shinichi Nogi, Sho Sasaki, Yasushi Koyama, Noriko Sasaki, Naofumi Chinen, Kiri Honda, Takayuki Wakabayashi, Chiho Yamada, Shinji Sato, Yasuo Suzuki

Tokai University School of Medicine

Conflict of interest: None

Anti-signal recognition particle (SRP) antibodies are one of myositis-

specific autoantibodies that are detected in 5-8% of polymyositis patients, and were generally associated with severe and refractory polymyositis. Here we report a Sjogren's syndrome patient who developed proximal muscle weakness with the marked elevation of serum creatine kinase (CK) and aldolase. Electromyogram showed myogenic change and muscle biopsy revealed infiltration of inflammatory cells and necrosis and regeneration of muscle fibers. Immunological examination revealed that she had anti-SRP antibodies by screening of RNA immunoprecipitation assay. Together, these findings resulted in a diagnosis of polymyositis (PM). Thereafter, 60mg of prednisolone daily was initiated. However, as her muscle weakness and serum CK concentration did not improve, we added 8mg of methotrexate weekly that led to the improvement of muscle symptom. In this case, autoantibodies examination was useful to determine the management of PM.

### P1-182

#### A case of a young woman developed malignancy-associated dermatomyositis with anti-TIF1- $\gamma$ antibody

Hirotaaka Itoh, Sohei Funakoshi, Masaki Katayama  
Osaka Red Cross Hospital

Conflict of interest: None

A 23-year-old Japanese woman suffered rash at back of hand and lower limbs, and muscle weakness of lower limbs. She had past history of the hepatoblastoma when she was 6 months old. She doesn't have any family history. She had lip edema and difficulty of opening mouth. Dermatomyositis was suspected from elevation of myogenic enzyme. She had erythema on her face and limbs, shawl sign and V neck sign with desquamation. The result of muscle biopsy was normal, but we diagnosed her as dermatomyositis from the results of MRI and electromyogram. She didn't have any antibodies which we can measure in general clinic and interstitial pneumonia, but anti-TIF1- $\gamma$  antibody was found from her serum by immunoprecipitation. As her skin symptom was severe, we thought lip edema was a kind of skin symptom. Advanced colon cancer and metastases to liver and pancreas were revealed by colon fiber and abdominal CT. Oral corticosteroid therapy had already initiated, but remission was not achieved. After initiation of steroid pulse therapy and anti-cancer therapy, she achieved remission. Her tumor became small with cancer treatment and dermatomyositis keeps remission.

### P1-183

#### A case of anti-SRP and anti-Ku-positive patient developed muscle weakness and amyotrophy without serum elevation of creatin kinase

Misato Kawakami<sup>1</sup>, Koichiro Horie<sup>1</sup>, Hidefumi Fukuda<sup>1</sup>, Kanako Iwata<sup>2</sup>, Hirotaaka Tsuno<sup>1</sup>, Hideki Ogihara<sup>1</sup>, Atsushi Hashimoto<sup>1</sup>, Akiko Komiya<sup>3</sup>, Toshihiro Matsui<sup>1</sup>, Shigeto Tohma<sup>2</sup>

<sup>1</sup>Department of Rheumatology, Sagamihara National Hospital, National Hospital Organization, <sup>2</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, National Hospital Organization, <sup>3</sup>Department of Clinical Laboratory, Sagamihara National Hospital, National Hospital Organization

Conflict of interest: None

We report a case of anti-SRP and anti-Ku positive 67 year old female patient who developed muscle weakness and amyotrophy in 3 months without elevation of serum creatin kinase (CK). Physical exam revealed muscle weakness of proximal limbs and neck, amyotrophy of limbs, and joint pains of limbs on motion. Cutaneous symptom and swelling joint were not found. Laboratory studies showed high level of serum CRP (4.4mg/dl) without elevation of serum CK and aldolase. Electromyography showed myographic change. There were no signs of malignancy and Gallium-67-schintigram only revealed inflammation around limb joints. Following muscle biopsy she was treated with predonisolone (PSL) 20mg/day (0.4mg/kg/day). Anti-SRP and anti-Ku positive were revealed after the induction of steroid treatment. Within seven days of steroid therapy, her muscle weakness and joint pains improved, and CRP level fell to normal. The muscle biopsy showed nonspecific findings, neither signs of degenerating, regenerating fibers, nor inflammatory infiltrations were detected. Tapering of PSL was started following one month of initial dose

and now she is treated with PSL 12mg/day. Muscle weakness, joint pains on motion, and elevation of serum CRP level did not appear during the course of steroid treatment.

### **P1-184**

#### **A case of dermatomyositis with anti MDA5 antibody positivity concomitant with severe myalgia and arthralgia and rapidly progressive interstitial lung disease**

Takashi Kato

Division of Rheumatology, Yamachika Memorial Hospital

Conflict of interest: None

A 57-year-old Japanese man had suffered from high-fever accompanied by severe myalgia and arthralgia two-week before admission. Proximal myalgia and arthralgia were so intensive that he could not move independently. Muscle weakness was absent but wrists were swollen. Skin lesions such as heliotrope rash and Gottron's sign were observed. Mild respiratory failure was observed, and findings of interstitial pneumonia on chest CT scan were detected. Laboratory findings were as follows; CK 530 IU/L, aldorase 6.8 U/L, KL-6 813 U/mL and ferritin 2,990 ng/mL. Concerning serological findings, ANA was 1: 40 (speckled). RF, anti CCP, anti Jo-1 nor anti ANCA was negative. Although myalgia was apparent in this case, a diagnosis of clinically amyopathic dermatomyositis (CADM) with rapidly progressive interstitial lung disease (RP-ILD) was considered. Thus, treatment with high dosage corticosteroid concomitant with intravenous cyclophosphamide and oral tacrolimus was commenced immediately. Nonetheless, RP-ILD remained progressive and the patient died on day 21. Later, positivity of anti MDA5 was revealed. Although DM with anti MDA5 (CADM-140) positivity commonly demonstrates amyopathic manifestations, findings in this case suggest that severe myalgia may occur in that condition.

### **P1-185**

#### **A case of anti-SRP myositis with asymptomatic high CK levels that anti-cytoplasmic antibody was useful for diagnosis**

Hirofumi Watanabe, Takaki Nojima, Hiroki Kono, Ayuko Sogabe, Satoshi Yamasaki, Kazuhiko Kumagai, Eiji Sugiyama  
Department of Clinical Immunology and Rheumatology, Hiroshima University Hospital, Hiroshima, Japan

Conflict of interest: None

A 68-year-old woman was admitted to our hospital because of elevated CK. Physical examination on admission showed no evidence for muscle involvement or neurologic abnormalities. Laboratory data revealed that her CK was elevated to 2375 U/l. ESR and CRP were both normal. Tests for anti-nuclear antibody, anti-ARS antibody and anti-Jo-1 antibody were all negative. But anti-cytoplasmic antibody was positive. Needle electromyogram at both rectus femoris muscle showed early recruitment. Muscle biopsy showed a small number of degenerating and regenerating fibers without inflammatory infiltrations. Positive test for anti-cytoplasmic antibody in her sera prompted us to test RNA immunoprecipitation assay and anti-SRP antibody was detected. Finally we diagnosed her as anti-SRP antibody positive polymyositis. [Clinical significance] We experienced a case of polymyositis with positive anti-SRP antibody. It was difficult to make diagnosis because there was neither muscle symptom nor inflammatory reaction. Positive test for anti-cytoplasmic antibody gave us a hint for diagnosis. We discuss about clinical features of anti-SRP antibody positive myositis and clinical importance of anti-cytoplasmic antibody in polymyositis.

### **P1-186**

#### **A dermatomyositis patient with anti-PL-7 antibody positive developed cancer of unknown primary site and died of diffuse alveolar hemorrhage**

Kyosuke Abe, Goh Tsuji, Mayuko Izumi, Ryosuke Umeda, Ai Muta, Yoshihide Ichise, Shunichi Kumagai  
Department of Rheumatic Disease Shinko Hospital, Hyogo, Japan

Conflict of interest: None

[Introduction] Coexistence of dermatomyositis (DM) and malignant conditions have been often reported. Few studies described the relation between anti-PL7 antibody and malignancy. We report a case of anti-PL7 positive DM, having malignant ascites, died of the diffuse alveolar hemorrhage (DAH). <Case> A 61-years-old man had gradually developed dry cough, myalgia and arthralgia three years before coming to our hospital. Physical examination, laboratory studies, radiographic and electromyography findings and the result of muscle biopsy led us to diagnose him as DM. Whole-body computed tomography, tumor markers, upper endoscopy and colonoscopy showed no malignant signs. Oral prednisolone therapy (1mg/kg/day) could improve his myositis insufficiently. On day 33, he developed thrombotic microangiopathy (TMA) and underwent plasma exchange therapy. Nevertheless gastrointestinal bleeding was seen on day 55 and DAH was appeared on day 77. After another plasma exchange and steroid pulse therapy, he died on day79. Cytology test of bloody ascites on day 73 revealed Class V of adenocarcinoma. Pathology dissection could not identify the primary site of cancer. Later, only anti-PL-7 antibody was detected, while the other ARS antibodies were negative.

### **P1-187**

#### **A case report of ulcerative colitis that developed following Takayasu's arteritis**

Yukari Endo<sup>1</sup>, Taiki Ando<sup>1</sup>, Go Murayama<sup>1</sup>, Yuri Yamazaki<sup>2</sup>, Shinya Kawano<sup>1</sup>, Yutaka Nakiri<sup>2</sup>, Ken Yamaji<sup>1</sup>, Naoto Tamura<sup>1</sup>, Yoshinari Takasaki<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology Juntendo University School of Medicine, <sup>2</sup>Department of Internal Medicine and Rheumatology Juntendo University School of Medicine, Nerima, Tokyo, Japan

Conflict of interest: None

A 35-year-old female with a past history of Takayasu's arteritis (TA), which improved with prednisolone (PSL) treatment (20 mg/day) and the dose of PSL was gradually decreased, had fever, diarrhea and abdominal pain from second-born childbirth. The patient was diagnosed with ulcerative colitis (UC) based on Endoscopic Examination, which revealed severely inflamed colonic mucosa, and Biopsy histology. Fever and diarrhea and abdominal pain were improved gradually with prednisolone and 5-aminosalicylic acid therapy. The result of human leukocyte antigen typing analysis was A24 and B52 positive. These findings suggested that common genetic factors may be important for the etiology of TA, UC. This is a case report of UC that developed following TA.

### **P1-188**

#### **A case of the elderly onset Takayasu's type giant cell arteritis with the brainstem infarction detected by 18FDG-PET/CT**

Yoshiko Sumita, Mayuko Moriyama, Masahiro Kondo, Yohko Murakawa  
Department of Rheumatology, Faculty of Medicine, Shimane University, Shimane, Japan

Conflict of interest: None

We describe a 73-year-old woman who presented due to left hemiplegia of acute onset. Physical examination revealed left hemiplegia, the paresthesia of left hand and dysarthria. By brain imaging, she was diagnosed with cerebral infarction of the right pons. She had an anemia as well as elevation of the ESR and CRP levels. At first, clinical symptoms were suspicious of malignant or septic disease. Extensive examination including rheumatological and microbiological assessment, ultrasonography (US) of abdomen, computed tomography (CT) of thorax and abdomen did not indicate any malignant or septic focus. By the contrast enhanced CT of thorax and abdomen, she was revealed the wall thickening of the aorta. She had not thickening and induration of the temporal artery, muscle pain and jaw claudication. There was no halo sign of the temporal artery in US. Finally, 18FDG-PET/CT was able to reveal arteritis of her aortic arch and supraaortic branches. Giant cell arteritis (GCA) was suspected, and treatment with high-dose prednisolone was initiated, clinical symptoms were markedly improved. This case confirms that 18FDG-PET/CT might serve as a valuable tool for diagnosis of giant cell arteritis, because it could facilitate an accurate and non-invasive detection of lesions of large vessels.

### P1-189

#### Golimumab for the refractory Takayasu arteritis

Ayako Fujimoto, Eiko Miyagawa, Komei Sakata, Mikako Iwakura, Koyu Hoshino, Shinya Hirata

Department of Rheumatology and Clinical Immunology, Kumamoto University Hospital, Kumamoto, Japan

Conflict of interest: None

[Objectives] Takayasu arteritis is a nonspecific vasculitis and is generally treated by high-dose steroid. Although immunosuppressant agents are used additionally, it is reported to use biological agents for the refractory cases. [Case] A 20 years old woman was admitted for fever and numbness on her right side in December 2010. As elevation of CRP and obstruction of some parts of arteries were detected by MRI, she was diagnosed as Takayasu arteritis. After 1 mg/kg of prednisolone (PSL) was administered, her condition was improved immediately. Her disease activity worsened when PSL was tapered to 20mg/day. Therefore, one or a pairs of azathioprine, Methotrexate (MTX), infliximab (IFX) and tocilizumab (TCZ) were administered. However, in April 2014, chest pain appeared when she was treated with PSL 10mg/day, TCZ 8mg/kg/month and MTX 14mg/week. Arterial stenosis and its wall thickness were exacerbated at the time. We switched TCZ to golimumab (GLM), and her symptom was improved consequently. [Consideration] We experienced the case that GLM was effective for refractory Takayasu arteritis resisted to various biological agents. This is an intractable case and we need to follow her clinical course more carefully.

### P1-190

#### Successful golimumab therapy in three patients with refractory Takayasu's Arteritis

Rie Suematsu<sup>1</sup>, Satoko Tashiro<sup>1</sup>, Yukihide Ono<sup>1</sup>, Yukiko Tokuda<sup>1</sup>, Yuri Sadanaga<sup>1</sup>, Nobuyuki Ono<sup>1</sup>, Syuichi Koarada<sup>1</sup>, Akihide Ohta<sup>2</sup>, Yoshifumi Tada<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Saga University School of Medicine, Saga, Japan, <sup>2</sup>Department of Adult & Gerontological Nursing, Saga University School of Medicine, Saga, Japan

Conflict of interest: None

Takayasu's arteritis (TA) is a rare granulomatous vasculitic disease that affects the aorta and its major branches. Recent studies have suggested that anti-TNF $\alpha$  biological therapies are highly effective in treating TA refractory to conventional immunosuppressive therapy. However there is no literature that reported the efficacy of golimumab (GLM) for TA. We report on three women with TA successfully treated with GLM. Case 1 developed TA that was resistant to glucocorticoid (GC) and methotrexate (MTX). She was treated with GLM for the first biologic therapy, and her TA led to remission after first GLM injection. Case 2 was with a 5-year history of TA resistant to GC and immunosuppressant, and her disease was in remission with infliximab (IFX) and MTX. We switched anti-TNF therapy from IFX to GLM, because the patient wished subcutaneous injection. Her TA has been in sustained remission thereafter. Case 3 showed active TA despite treatments with IFX, adalimumab, and tocilizumab. However, her TA remitted with GLM (100mg) and MTX (16mg/week). Taken together, GLM might be useful, as well as other anti-TNF agents, in treating TA.

### P1-191

#### Analysis of clinical feature of giant cell arteritis in five cases

Koichiro Taguchi<sup>1</sup>, Daisuke Murakami<sup>1</sup>, Kei Fujioka<sup>1</sup>, Ichiro Mori<sup>2</sup>, Tatsuo Ishizuka<sup>1</sup>

<sup>1</sup>Center of General Internal Medicine and Rheumatology, Gifu Municipal Hospital, Gifu, Japan, <sup>2</sup>Department of General Internal Medicine, Gifu University Graduate School of Medicine, Gifu, Japan

Conflict of interest: None

[Objectives] We studies on 5 cases of Giant cell arteritis (GCA). [Methods] GCA was diagnosed by ACR classification criteria (1990) from April, 2011 to November, 2014. [Results] 4 female and one male: average age 79 years, average BMI 20.8. Symptoms were headache (4

cases), fever (4 cases), PMR symptoms (3 cases), jaw claudication (3 cases), edema (2 cases), loss of weight (2 cases), oculomotor nerve paralysis (1 case), vision loss (1 case), ischemic findings in ocular fundus (2 cases), and interstitial pneumonia (1 case). Elevated CRP and ESR (all cases), hyperferritinemia (all cases), anemia (4 cases), thrombocytosis (4 cases), Abnormal temporal artery ultrasonography findings (3 cases) were observed. The initial treatment dosage was as follows: PSL 1 mg/kg/day (3 cases), mPSL pulse (1 case), PSL 30 mg/day (1 case). Response to treatment was good in all cases, and period for normalization of CRP levels was 15.8 days. Aspirin and Sulfamethoxazole/trimethoprim were administered concurrently in 3 cases, respectively. Adverse effects were steroid diabetes, candidiasis, tuberculosis, osteoporosis, venous thromboembolism. [Conclusion] Because of low sensitivity for diagnosis by ultrasonography, temporal artery biopsy should be examined. Adverse effects occurred high frequently.

### P1-192

#### A Case of giant cell arteritis, presenting a contrast enhancement of large vessel wall in magnetic resonance imaging

Norihiro Nagamura

Department of Rheumatology and Allegy, Shimane Prefectural Central Hospital, Izumo, Japan

Conflict of interest: None

A 79-year-old female had a persistent fever and realized nuchal stiffness and right shoulder pain six month before. She consulted her family doctor and was given medicine of antibiotics. The medication wasn't effective for the improvement of her symptoms, therefore she was referred to our hospital for close examination. On the first physical examination, she had no skin eruption nor arthritis nor tenderness and hypertrophy of temporal artery. By contrast enhanced magnetic resonance imaging (CE-MRI) of her right shoulder, subacromial bursitis and wall inflammation from axillary to brachial artery were observed. She had no peripheral neuropathy, we suspected giant cell arthritis (GCA) and performed biopsy of temporal artery. The histopathological findings supported the diagnosis of GCA. GCA is classified as large vessel vasculitis and some cases show negative histopathological finding of temporal arteritis. The CE-MRI finding of arterial wall in inflammatory phase is the useful finding for the diagnosis of GCA.

### P1-193

#### A Case of silent type Giant Cell Arteritis: PET/CT was only effective for its diagnosis

Michihito Katayama, Toru Hirano, Kentaro Fujii, Hideki Yorifuji, Atsuyoshi Morishima, Yoshihito Shima, Atsushi Kumanogoh  
Respiratory Medicine, Allergy and Rheumatic Disease, Graduate School of Medicine, Osaka University, Osaka, Japan

Conflict of interest: None

We introduce a patient with persistent high fever. Her previous doctor has examined her minutely, but no symptom of particular disease was detected. We took Positron-Emission Tomography- Computed Tomography and find accumulation of fluorodeoxyglucose at aorta and its branches. We diagnosed her as giant cell arteritis. There were some reports of subtypes of giant cell arteritis. We will report this case and a review of subtypes of arteritis.

### P1-194

#### Cerebellar infarction shortly after initiation of corticosteroid treatment in a patient with giant cell arteritis

Yukinari Yamaguchi<sup>1</sup>, Koji Harada<sup>1</sup>, Juri Tsukahara<sup>1</sup>, Koichi Sumida<sup>1</sup>, Yasuhiro Akai<sup>2</sup>

<sup>1</sup>Department of Nephrology and Rheumatology, Rakuwakai Otowa Hospital, <sup>2</sup>Center for Rheumatic Disease, Nara Medical University Hospital

Conflict of interest: None

Case report: A 74 years male was admitted for persistent temporal headache and jaw claudication. He was diagnosed as giant cell arteritis

(GCA) according to the ACR classification criteria. Glucocorticoid was started with satisfactory improvement of cephalic symptoms. Five days after initiation of corticosteroid treatment vertigo and muscle weakness of the right lower limb developed. MRI showed fresh cerebellar infarction in the area of the left posterior inferior cerebellar artery (PICA), and MR angiogram revealed the stenosis of right vertebral artery. Because of the absence of atrial fibrillation and intracardiac thrombi, his cerebellar infarction was thought to be associated with the right vertebral artery stenosis. After antiplatelet and fluid therapy was initiated, neurological symptoms gradually resolved. Summary: The GCA patients who complicated with cerebral vascular disease have been rarely reported. We would report this case with literature review for the association between GCA and cerebral vascular disease.

### P1-195

#### **An example of the polyarteritis nodosa, which happened the cellulitis due to the fulminant form group A streptococci infection**

Takayoshi Tsukahara, Kurisu Tada, Hirofumi Amano, Ken Yamaji, Naoto Tamura, Yoshinari Takasaki

Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine, Tokyo, Japan

Conflict of interest: None

**[Case]** 56 years old, male **[chief complaint]** lower right thigh swelling **[Clinical history]** In 1999, muscle ache and appendicular numbness developed and a subcutaneous nodule appeared in right upper arm. He was made a diagnosis of polyarteritis nodosa from the biopsy of the site in another hospital. We made start of therapy with 30mg/day of prednisolone and symptoms were light. We lost weight to 12mg/day and condition was stable. In July, 2014, the right calf showed swelling and pain. Laboratory data showed leukocyte 20000/ $\mu$ L, CRP 35.5mg/dl, Procalcitonin 52.3ng/ml, so he was considered severe sepsis due to the cellulitis. When it was on admission, he was a state of the shock and we started MEPM and CLDM. After that, A group hemolytic streptococcus was detected by blood cultures, so we switched to PCG. The therapeutic response was good and he became the discharge on the 38th day of illness. This infection was regarded as streptococcal toxic shock syndrome (STSS). **[Discussion]** STSS causes multiple organ failure, shock for several hours and its mortality is over 30%. We added up 45 cases for soft tissue infection that needed hospitalization in our hospital in the past 5 years. The number of cases of STSS is two (4.4%). When immunosuppressive treatment is provided, it is one of the considerable infection.

### P1-196

#### **Clinical features of ANCA associated vasculitis in Kochi**

Koji Ogata, Taro Horino, Tatsuki Matsumoto, Kazu Ode, Yoshiko Shimamura, Kosuke Inoue, Yoshinori Taniguchi, Yoshio Terada  
Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi University

Conflict of interest: None

**[Objectives]** Our goal is to assess the clinical features of ANCA associated vasculitis in Kochi Prefecture. **[Methods]** 20 patients who had been admitted to our hospital as a central hospital of Kochi Prefecture from 2010 to 2014 were enrolled. All patients met the Watt's criteria for vasculitis. We assess the correlation between the clinical characteristics and data. **[Results]** Female were 12 (60%). Mean age was 74.3 years old. All patients had positive MPO-ANCA test, while only one had positive PR3-test. Clinical data and biopsy specimen revealed that renal and lung complications were observed in 17 (85%) and 16 (80%) patients, respectively. According to Watt's algorithm, EGPA, GPA and MPA patients were 5 (25%), 3 (15%), and 12 (60%), respectively. Laboratory data on admission showed that average values were as follows; Cr was 2.03 mg/dl, BUN was 30.0 mg/dl, LDH was 200.8 $\pm$ 5.6 U/ml, Cr was 0.67 $\pm$ 0.03 mg/dl, BUN was 15.2 $\pm$ 0.5 mg/dl, CRP was 7.29 mg/dl, and MPO-ANCA was 365.1 IU/ml. Intensive therapies included mPSL pulse therapy (65%) and IVCY (25%), following oral PSL (average dose was 40.5 mg daily). Almost patient had good prognosis, except only one patient. **[Conclusion]** Our data suggests that in Kochi Prefecture, patients might be elder and female and have positive titer of MPO-ANCA test.

### P1-197

#### **Measurement of serum ANCA titer: useful predictor of relapse in MPO-ANCA-associated glomerulonephritis with systemic vasculitis**

Yoshinobu Fuke, Seiichiro Hemmi, Mamiko Kajiwara, Takayuki Fujita, Masayoshi Soma

Department of Medicine, Division of Nephrology, Hypertension and Endocrinology, Nihon University School of Medicine, Tokyo, Japan

Conflict of interest: None

**[Objectives]** We evaluated the predictive value of ANCA as markers of relapse in patients with MPO-ANCA associated glomerulonephritis. **[Methods]** The medical history of 26 consecutive patients with MPO-ANCA associated glomerulonephritis followed at our hospital for more than 6 months were retrospectively reviewed. **[Results]** During a median follow-up period of 37.9 months, ANCA rises in 13 patients and relapses in 7 patients were recorded, and ANCA rises correlated with relapses (Odds ratio 10.2,  $p$ <0.05). Clinical features of the relapses included 6 fevers, 3 lung involvements, 3 decreased renal functions, 1 neuron involvement, and 1 large intestine hemorrhages. Relapse occurred in 6 patients (40%) with systemic vasculitis (S-group) but in only 1 patient (8%) with kidney-limited vasculitis (K-group), although ANCA rise ratio was 46% in S-group and 63% in K-group, respectively. ANCA rises correlated with relapses in S-Group (Odds ratio 17.5,  $p$ <0.05). **[Conclusion]** Measurement of serum ANCA titer may be useful predictor of relapse only in MPO-ANCA-associated glomerulonephritis with systemic vasculitis.

### P1-198

#### **Oxidative modification of myeloperoxidase in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides**

Teisuke Uchida<sup>1</sup>, Kohei Nagai<sup>2</sup>, Toshiyuki Sato<sup>3</sup>, Seido Ooka<sup>1</sup>, Mitsumi Arito<sup>3</sup>, Shoichi Ozaki<sup>1</sup>, Manae S. Kurokawa<sup>4</sup>, Tomohiro Kato<sup>3</sup>

<sup>1</sup>Division of Rheumatology and Allergy, Department of Internal Medicine, St. Marianna University School of Medicine, <sup>2</sup>Department of Genetic Engineering, Faculty of Biology-Oriented Science and Technology, Kinki University, <sup>3</sup>Clinical Proteomics and Molecular Medicine, St. Marianna University Graduate School of Medicine, Kawasaki, Japan, <sup>4</sup>Disease Biomarker Analysis and Molecular Regulation, St. Marianna University Graduate School of Medicine

Conflict of interest: None

**[Objectives]** Alteration of post-translational modifications of myeloperoxidase (MPO) was examined in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides. **[Methods]** Protein was extracted from peripheral blood polymorphonuclear cells (PMN) obtained from 5 MPO-ANCA-positive patients with ANCA-associated vasculitides and 5 healthy donors. MPO was detected by 2-dimensional western blot (2D-WB). **[Results]** Heavy and light chains of MPO from healthy donors were detected respectively as multiple protein spots by 2D-WB. Intensity of heavy chain spots that showed higher isoelectric points (pI) and heavier molecular weights than its theoretical values (pI 9.4, 53kDa) was significantly higher in the MPO-ANCA-positive group than the healthy group ( $p$ <0.01). Treatment of PMN protein from healthy donors with reactive oxygen species (ROS) showed similar 2D-WB results with those of the MPO-ANCA-positive group. In 1D-WB results, dityrosine bands indicating oxidative modification were detected in the PMN protein from MPO-ANCA-positive patients and the ROS-treated PMN protein, but not in the non-treated PMN protein from healthy donors. **[Conclusion]** MPO was oxidatively modified in MPO-ANCA-positive patients. This modification may participate in the production of MPO-ANCA.

### P1-199

#### **Comparison of respiratory organ involvement and clinical course on the basis of ANCA subtype**

Takeo Sato, Takamasa Murosaki, Yoichiro Akiyama, Katsuya Nagatani, Seiji Minota

Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Jichi Medical University, Tochigi, Japan

Conflict of interest: None

[Background] Clinical characteristics of ANCA-associated vasculitis (AAV) are evaluated mainly clinically. Recent studies revealed that the genetic background of MPO-ANCA positive AAV (MPO-AAV) and PR3-ANCA positive AAV (PR3-AAV) differs. [Objective] To clarify the difference in respiratory organ involvement which is critical for prognosis between MPO-AAV and PR3-AAV. [Method] We selected in- or out-patients with MPO-AAV and PR3-AAV from 2005 to October 2014. We compared their clinical characteristics, imaging findings, and progression to respiratory failure. [Result] We found 85 patients with MPO-AAV and 17 with PR3-AAV. Respiratory organ involvements were as follows: the presence of respiratory involvement 71 vs. 14 ( $p=1.0$ ); interstitial pneumonia 42 vs. 1 ( $p<0.001$ ); airway lesion 11 vs. 0 ( $p=0.20$ ); nodular lesion 7 vs. 9 ( $p<0.001$ ); alveolar hemorrhage 5 vs. 3 ( $p=0.13$ ); and asthma 9 vs. 2 ( $p=1.0$ ), respectively. The probabilities of respiratory failure free survival at 10 years were 0.52 and 1.0 ( $p=0.089$ ). [Conclusion] The incidence of respiratory organ involvement in two AAVs was similar, but there were some differences in clinical characteristics. ANCA subtype may be as important as disease classification clinically.

### P1-200

#### Analysis of ANCA testing contribution to diagnosis of ANCA associated vasculitis

Eishi Uechi, Chia Nakata, Tomoo Murayama, Yoshiki Shiohira  
Tomishiro Central Hospital, Okinawa, Japan

Conflict of interest: None

[Objectives] We examined the diagnostic value of ANCA testing to diagnose of ANCA associated vasculitis in use of our hospital data. [Methods] We examined by data of MPO-ANCA or PR3-ANCA testing performed in Tomishiro central hospital in Okinawa between 2009 to 2014. We analyze the patients' clinical diagnosis, clinical symptom. [Results] We extract 2783 ANCA testing, 2019 patients who have testing between 2009 to 2014. 107 (7.1%) patients are MPO-ANCA positive, 36 (1.8%) patients PR3-ANCA positive. In MPO-ANCA positive patients, microscopic polyangitis are 30 patients (28%), granulomatous polyangitis 1 (0.9%), eosinophilic polyangitis 2 (1.87%). In PR3-ANCA positive patients, microscopic polyangitis are 2 patients (5.6%), granulomatous polyangitis 1 (2.8%), eosinophilic polyangitis is none. [Conclusion] In clinical setting, either specialists or non-specialists test many patient for MPO-ANCA or PR3-ANCA. But those test's positive rate is less than ten percent. Most of patients who have ANCA positive are diagnosed of non-ANCA associated vasculitis. We select the patients who have high pre-test probability of ANCA associated vasculitis before testing ANCA. It is important that when ANCA positive, we interpret the ANCA test with caution.

### P1-201

#### Efficacy and safety of combination therapy with glucocorticoid plus immunosuppressant in patients with MPO-ANCA positive ANCA associated vasculitis

Ryutaro Yamanaka, Hidetoshi Kagawa  
Department of Internal Medicine, Himeji Red Cross Hospital, Himeji, Japan

Conflict of interest: None

[Objectives] To study Efficacy and safety of combination therapy with glucocorticoid plus immunosuppressant in patients with MPO-ANCA positive ANCA associated vasculitis. [Methods] We retrospectively studied 29 patients with MPO-ANCA positive ANCA associated vasculitis who were diagnosed in our hospital since January 2007. [Results] There were 13 males and 16 females. The mean age $\pm$ SD of onset was 69.9 $\pm$ 9.0 years old. Renal involvement, pulmonary involvement and polyneuropathy was present in 27 cases, 16 cases and 15 cases. 13 patients received m-PSL pulse therapy. The mean initial dose of PSL was 51.4 $\pm$ 13.3mg/day. 22 patients received IVCY as remission induction therapy. 15 patients treated with immunosuppressant (AZA: 8, MZR: 6, TAC: 1) as remission maintenance therapy. The initial level of MPO-ANCA $\pm$ SD was 239.9 $\pm$ 175.3EU. All patients achieved a remission. 8 patients were relapsed. 3 patients were died. The rate of combination therapy with PSL plus immunosuppressant as remission induction therapy and

remission maintenance therapy was higher in 18 patients after April 2011 than in 11 patients before. [Conclusion] The combination therapy with glucocorticoid plus immunosuppressant was effective in patients with MPO-ANCA positive ANCA associated vasculitis.

### P1-202

#### Two cases of bacterial infection with elevation of MPO-ANCA

Mayuko Izumi<sup>1</sup>, Ai Muta<sup>1</sup>, Kyosuke Abe<sup>1</sup>, Ryosuke Umeda<sup>1</sup>, Yoshihide Ichise<sup>1</sup>, Sho Sendo<sup>2</sup>, Goh Tsuji<sup>1</sup>, Shunichi Kumagai<sup>1</sup>

<sup>1</sup>Department of Rheumatic Disease Shinko Hospital, Hyogo, Japan, <sup>2</sup>Department of Rheumatic Disease, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan

Conflict of interest: None

[Case 1] A 82-year-old female was suffered from polyarthritis and fever. Diffuse granular image on computed tomography was compatible with diffuse panbronchiolitis. Her sputum culture revealed with *Pseudomonas aeruginosa*, and antibiotics therapy was started. She came to our hospital due to ineffective of antibiotics therapy and the elevation of MPO-ANCA. Corticosteroids were administered for her arthritis and myalgia, though she did not meet the diagnostic criteria of ANCA associated vasculitis (AAV). Immediately all of her symptoms improved, nevertheless the MPO-ANCA was not decrease. [Case 2] A 89-year-old female was diagnosed as pyelonephritis and administered with antibiotics. She was admitted to our hospital because of high fever and the elevation of MPO-ANCA. She also didn't meet the diagnostic criteria of AAV nor have the organ damage related with vasculitis. Positive result of CD toxin test led us to diagnose her as *Clostridium difficile* infection. Though vancomycin therapy decreased her high fever, her MPO-ANCA was not normalized. [Discussion] We experienced two cases of bacterial infected patients, whose MPO-ANCA elevated. Both of two cases did not meet the AAV criteria. Some of microorganisms can induce ANCA production of hosts and concerned with the onset of AAV.

### P1-203

#### Three cases of the young onset ANCA-associated vasculitis

Keisuke Horikoshi, Takahiro Yuasa, Keisuke Sako, Shohei Makiishi, Taro Miyagawa, Akihiro Sagara, Yasuyuki Shinozaki, Shinji Kitajima, Akinori Hara, Yasunori Iwata, Norihiko Sakai, Miho Shimizu, Kengo Furuichi, Takashi Wada

Department of Nephrology, Kanazawa University Hospital

Conflict of interest: None

[case1] A 15 years old female was indicated proteinuria, hematuria, Cre 15.1 mg/dL and the positivity of MPO-ANCA. Renal biopsy specimen revealed the crescent formation of all of the glomerulus. Thus, she was diagnosed with AAV. She was performed steroid pulse and plasma exchange. However, the renal function was not improved, and she has been treated with maintenance hemodialysis. [case2] A 18 years old female was indicated proteinuria, hematuria, Cre 0.9 mg/dL and the positivity of MPO-ANCA. Renal biopsy showed the crescent formation in 16 of 17 glomerulus. Thus, she was diagnosed with AAV. She was treated with steroid pulse, resulting in the clinical remission. However, renal function was gradually worsened with two times of relapse. She has been treated with hemodialysis when she was 31 years old. [case3] A 13 years old female was diagnosed with IgA nephropathy by renal biopsy. When she was 20 years old, blood test showed the worsened renal function with positivity of MPO-ANCA. We performed renal biopsy again, and Kidney specimen showed the crescent formation in 7 of 12 glomerulus. Thus, she was diagnosed with AAV. She was treated with steroid and renal function has been kept. [summary] We experienced three cases of the young onset AAV, which was relatively rare in vasculitis.

### P1-204

#### Nephrotic syndrome due to ANCA related vasculitis combined with IgA nephropathy

Akira Jibatake, Tamao Nakashita, Shinji Motojima  
Kameda Medical Center, Kamogawa, Chiba, Japan

Conflict of interest: None

[Objectives] IgA nephropathy could be the cause of hematuria and proteinuria, but rare to cause nephrotic syndrome. otherwise, IgA nephropathy and ANCA-related vasculitis are the main causes of glomerulonephritis with the feature of crescent body, but a few cases of ANCA-related vasculitis occurring with IgA nephropathy have been reported. [case] A 68-year-old female who has a history of subclinical hematuria for ten years presented to our hospital with her mammary tumor. As the urinary test showed hematuria and proteinuria, she was consulted to our department. urinary protein<sup>3+</sup>, hematuria with no cast, 5.3g urine protein estimated. TP5.4g/dL, Alb2.6g/dL, ANA320, anti SS-A body negative, IgA382mg/dL, normal complement, MPO-ANCA36.6RU/ml. loop and mesangium composure of half moon body and IgA by kidney biopsy and diagnosed it with ANCA-related vasculitis and IgA kidney disease. After a breast cancer resection, steroid afterwards. [Conclusion] Each IgA kidney disease and ANCA-related vasculitis caused the glomerulonephritis, but thought that it was necessary to perform a biopsy on kidney in the ANCA-positive example, and to definitively diagnose it because convalescence was different from a cure

### P1-205

**Nephropathy complicated both ANCA-associated vasculitis and SLE**  
Komei Sakata, Ayako Fujimoto, Eiko Miyagawa, Mikako Iwakura, Koyu Hoshino, Shinya Hirata  
Departments of Hematology, Rheumatology and Clinical Immunology, Kumamoto University Hospital

Conflict of interest: None

[Introduction] Although systemic lupus erythematosus (SLE) and ANCA-associated vasculitis (AAV) are the rheumatic diseases which cause nephropathy. Generally, it is not so difficult to distinguish them by physical findings and examination results. It is rare to complicate both of them. [Case] A 52-years-old female visited our hospital on suspicion of SLE or AAV. She had sustained fever, dyspnea, anasarca, pleural and peritoneal effusions, proteinuria, nephropathy, high titer of MPO-ANCA, low titer of PR3-ANCA, ANA positive 1280 X (speckled pattern), anti-dsDNA positive, and hypocomplementemia. Nevertheless meeting the classification criteria for SLE, the renal biopsy diagnosis was crescentic glomerulonephritis, suggesting AAV. Finally we started the remission induction therapy, with prednisolone (PSL) 40 mg/day and intravenous cyclophosphamide pulse therapy (IVCY, 500 mg/body/two weeks) as 6 times. Albuminuria improved well, then we switched to azathioprine after the IVCY. No exacerbation was observed, in spite of tapering dose of PSL. [Discussion] We experienced the case of ANCA-associated nephropathy with SLE. As there is a few case reports complicated SLE and AAV which often described serious clinical course, we need to observe her clinical course more carefully.

### P1-206

**Comparison of serum beta 2-microglobulin level among vasculitis syndromes**  
Rika Okada, Shigeko Inokuma, Yoko Miura, Mika Kobuna, Masanobu Horikoshi, Shoko Kobayashi  
Japan Red Cross Medical Center Allergy and Rheumatology

Conflict of interest: None

[Background] Serum beta 2-microglobulin ( $\beta_2$ MG) level sometimes increases in collagen diseases. We reported serum  $\beta_2$ MG level did not increase in hypereosinophila-associated diseases. In this study, we compared the serum  $\beta_2$ MG level between eosinophilic granulomatosis with polyangiitis (EGPA) and other vasculitides. [Methods] Serum  $\beta_2$ MG level before treatment in patients who diagnosed with vasculitis syndromes from 2006 to 2014, was compared between EGPA and others. [Results] Twenty-two patients (11 males and 11females aged 69.4 $\pm$ 13.4; 5 EGPA and 17 others; microscopic polyangiitis, polyarteritis nodosa, temporal arteritis, granulomatosis with polyangiitis) were included. The mean level of serum  $\beta_2$ MG was significantly lower in EGPA than in others (2.2 $\pm$ 0.5 vs 6.1 $\pm$ 5.9 mg/L). As for cases which serum creatinine (Cre) level were  $\leq$ 1mg/dL, there was no statistical difference between EGPA and others

[2.2 $\pm$ 0.5 (n=5) vs 2.8 $\pm$ 0.6 (n=11) mg/L]. Compared in terms of serum  $\beta_2$ MG/Cre, no statistical difference was observed between EGPA and others (3.7 $\pm$ 0.4 vs 4.5 $\pm$ 1.8 mg/L). [Conclusion] The level of serum  $\beta_2$ MG was lower in EGPA than in others significantly. However, taking serum Cre level into consideration, no statistical difference was observed between EGPA and others.

### P1-207

**Three cases of probable localized granulomatosis with polyangiitis (GPA)**

Akiko Aoki<sup>1</sup>, Hiroshi Oka<sup>2</sup>

<sup>1</sup>Department of General Medicine, Tokyo Medical University Hachioji Medical Center, Tokyo, Japan, <sup>2</sup>Department of Rheumatology, Tokyo Medical University Hachioji Medical Center, Tokyo, Japan

Conflict of interest: None

[Objectives] Histological findings are essential to confirm the diagnosis localized granulomatosis with polyangiitis (GPA). Although nasal biopsy is limited by the high rate of false negative results due to the small amount of tissue that can be removed. We report three case of probable localized GPA with positive PR3-ANCA. [Patient 1]35-year-old man was treated with prednisolone 30mg/day for bilateral scleritis. He complained of hearing loss and generalized myalgia. [Patient 2]78-year-old woman was admitted to our hospital because of fever and polyarthralgia. She developed hearing loss and skin eruption. [Patient 3]64-year-old man, who had been treated for diabetes mellitus, hypertension and ischemic heart disease, was found to have left pleural effusion and lung parenchymal involvement by chest CT scan. All three cases were serum PR3-ANCA positive. However, the results of nasal biopsies showed neither granulomatous lesions nor vasculitis. Pleural and skin biopsies were negative in Patient 3. The diagnosis of three patients was probable GPA. Moderate doses of PSL were started in Patient 1 and 2. [Conclusion] There is controversy regarding the initiation of therapy without a confirming biopsy. The further studies are needed for therapy probable localized GPA.

### P1-208

**CD14-positive inflammatory monocytes may play a role in lymphoid follicle formation in IgG4-related disease**

Tomomi Sato<sup>1</sup>, Nozomu Kurose<sup>2</sup>, Takafumi Kawanami<sup>1</sup>, Takuji Nakamura<sup>1</sup>, Haruka Iwao<sup>1</sup>, Akio Nakajima<sup>1</sup>, Miyuki Miki<sup>1</sup>, Tomoyuki Sakai<sup>1</sup>, Yoshimasa Fujita<sup>1</sup>, Masao Tanaka<sup>1</sup>, Toshihiro Fukushima<sup>1</sup>, Yasufumi Masaki<sup>1</sup>

<sup>1</sup>Department of Hematology and Immunology, Kanazawa Medical University, <sup>2</sup>Department of Pathology and Laboratory Medicine, Kanazawa Medical University

Conflict of interest: None

The elevated IgG4 in patients with IgG4-related disease (IgG4-RD) is polyclonal, therefore the pathogenesis involves more important upstream events exist. We speculated that lymphoid follicle formation may play an important role in the pathogenesis of IgG4-RD, then we reassessed histopathological findings of each cell distribution in lymphoid follicle formation by immunostaining using various antibodies. Involved tissue samples from 22 patients with IgG4-RD, as well as control tissue samples from the lymph nodes of patients with reactive hyperplasia (n=3), lymph nodes of patients with multicentric Castleman's disease (n=3), and labial salivary glands of patients with Sjögren's syndrome (n=13) were examined. CD14-positive lymphoid follicles were observed only in tissue of IgG4-RD patients. There were few differences in the distributions of other cell types, such as resident monocytes or M1 and M2 macrophages between IgG4-RD and control groups. These observations suggested that the ectopic distribution of CD14+ inflammatory monocytes may play an important pathophysiological role in IgG4-RD.

### P1-209

**Importance of anti-nuclear antibody in IgG4-related disease**

Satoshi Hara, Shigeto Horita, Hiromi Nuka, Takeshi Zoshima, Kiyooki Ito, Motohiko Aizu, Hiroshi Fujii, Kazunori Yamada, Mitsuhiro Kawano

Conflict of interest: None

[Background & Objectives] Anti-nuclear antibody (ANA) is a major autoantibody widely detected in autoimmune disease. Some researchers speculate that IgG4-related disease (IgG4RD) is one autoimmune disease because ANA is also detected, but it remains undetermined how ANA is important in IgG4RD. The present study aimed to clarify the titer and staining pattern of ANA in IgG4RD. [Methods] We studied 70 patients diagnosed as IgG4-RD in our facility between April 1994 and October 2014. The titer and staining pattern of ANA using immunofluorescence in IgG4RD were retrospectively compared to 65 patients of systemic lupus erythematosus (SLE), 20 patients of anti-SS-A antibody positive Sjogren syndrome (SjS), and 341 people of healthy controls (HC). [Results] The titer of ANA was described as; 30.0% at >1:40 and 10.0% at >1:160 in IgG4RD; 100% at >1:40 and 86.4% at >1:160 in SLE; 95.5% at >1:40 and 86.4% at >1:160 in SjS; 30.9% at >1:40 and 1.5% at >1:160 in HC. The first major staining pattern of ANA was homogenous in IgG4RD, and speckled in SLE and SjS. [Conclusion] The titer and staining pattern of ANA in IgG4RD is different from that of SLE and SjS, and is similar to that of HC, suggesting that ANA is not useful in the diagnosis of IgG4RD.

### P1-210

#### Clinical characteristics and outcome of patients with IgG4-related disease

Mitsuteru Akahoshi<sup>1</sup>, Sho Ueda<sup>1</sup>, Shoichiro Inokuchi<sup>1</sup>, Tsuyoshi Nakayama<sup>1</sup>, Ayako Takaki<sup>1</sup>, Jin Nakagawa<sup>1</sup>, Shota Nakano<sup>1</sup>, Yuri Hiroaki<sup>1</sup>, Naoko Ueki<sup>1</sup>, Satomi Hisamoto<sup>1</sup>, Masahiro Ayano<sup>1</sup>, Shun-ichiro Ota<sup>1</sup>, Atsushi Tanaka<sup>1</sup>, Yojiro Arinobu<sup>1</sup>, Hiroaki Niiro<sup>2</sup>, Hiroshi Tsukamoto<sup>1</sup>, Koichi Akashi<sup>1</sup>

<sup>1</sup>Department of Clinical Immunology and Rheumatology and Infectious Disease, Kyushu University Hospital, Fukuoka, Japan, <sup>2</sup>Clinical Education Center, Kyushu University Hospital, Fukuoka, Japan

Conflict of interest: None

[Objectives] To examine clinical characteristics and outcome of patients with IgG4-related disease (IgG4-RD) [Methods] We retrospectively analyzed the data of 30 patients with IgG4-RD at Kyushu University Hospital from April 2006 to November 2014. [Results] Among 30 cases of IgG4-RD diagnosed according to IgG4-RD comprehensive and/or organ specific diagnostic criteria, 19 patients (63%) were male, average age was 64.2 years, 85% of the patients showed elevated serum IgG4 levels, and 42% had elevated serum IgE levels. Only 7% of IgG4-RD patients tested positive for antinuclear antibodies test (1:160 or more), and all patients were negative for anti-SS-A/SS-B tests. Lacrimal/salivary gland lesions were found in 80% of the patients, and other organ involvement such as lymph nodes, lung, retroperitoneum, and pancreas was detected with a relatively high frequency (approximately 40-20%). The complication of allergy or malignancy was found in 23% of the patients. Treatment with prednisolone was initiated with an average of 0.5-0.6 mg/kg/day, and steroid therapy can be stopped in 13% of the patients. Six (20%) of all patients have been followed without therapy. [Conclusion] The establishment of therapeutic algorithm/strategy for IgG4-RD according to the clinical condition is expected.

### P1-211

#### High variety of IgG4-related disease in terms of organ damages, treatment response, and life survival

Yuriko Yamamura<sup>1</sup>, Yoshihisa Nomura<sup>2</sup>, Kazuyuki Fujita<sup>1</sup>, Noriya Momoki<sup>2</sup>, Akiko Ueno<sup>1</sup>, Masahiro Yamamura<sup>1</sup>

<sup>1</sup>Center for Rheumatology, Okayama Saiseikai General Hospital, Okayama, Japan, <sup>2</sup>Center for Nephrology, Okayama Saiseikai General Hospital, Okayama, Japan

Conflict of interest: None

[Objectives] IgG4-related disease (IgG4-RD) is characterized by tissue infiltration of IgG4+cells and local fibrosis. To know the present sta-

tus of this systematic disease and its treatment and prognosis in practical clinic. [Methods] We have prospectively followed-up clinical courses of 31 patients (21 males and 10 females) with IgG4-RD at our hospital since 2011 April, essentially according to the 2011 Comprehensive Diagnostic Criteria. [Results] The average age of our cohort at diagnosis was 68.1 year-old (27-85 year-old). 20 patients had been initiated with corticosteroids (prednisolone: 21.7 mg/day on average) due to organ dysfunction such as pancreatitis, renal damages, and urinary tract obstruction. 11 patients were added with immunosuppressants such as azathioprine and methotrexate. Other 11 patients were followed-up without drug therapy, but they remained healthy. On the other hand, 3 patients were involved by MALT lymphoma, lung cancer, and colon cancer, and 2 patients died. [Conclusions] IgG4-RD was treatable with corticosteroids but its indication should be limited only patients with organ dysfunctions. The disease was highly variable in terms of outcomes such as organ damages, life survival, and treatment response.

### P1-212

#### Clinical evaluation of IgG4-related diseases in our department

Yasufumi Shindo, Yuji Akiyama, Yoshihiro Yoshida, Kazuhiro Yokota, Yasuto Araki, Hiroshi Kajiyama, Haruhiko Akiba, Kojiro Sato, Toshihide Mimura

Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Saitama, Japan

Conflict of interest: None

[Objectives] The fine clinical course and pathogenesis of IgG4-RD has not been wellknown. In this study, we clinically examined IgG4-RDs. [Methods] The patients were diagnosed as definite, probable or possible disease using the Comprehensive diagnostic criteria for IgG4-RD 2011. The clinical symptoms and laboratory data were retrospectively reviewed based on the medical records in our department. [Results] Patients were 11 males and 2 females. The average age at the diagnosis was 66.0 years old. The average serum IgG4 level before treatment was 654.46 (34~1850) mg/dl. Affected organs were; salivary glands 5, lacrimal glands 2, pancreas 3, retroperitoneum 1, abdominal aorta 1, and superior vena cava 1. Administered prednisolone (average 28.46mg/day) as initial therapy were in all cases. Corticosteroids were effective in all, except two cases that needed immunosuppressants (azathioprine and tacrolimus). Serum IgG4 levels were normalized in 12 cases and the size of lesions was reduced in all. Steroids were effective in most of cases. The responsiveness of corticosteroids against IgG4-RDs was good in our department. Serum IgG4 levels were normalized in 12 and the size of lesions was reduced in all. [Conclusion] Corticosteroid were effective and could be tapered in many cases.

### P1-213

#### A case of IgG4-related disease presented with urinary tract obstruction alone

Kazutoshi Yukawa, Kensuke Irino, Asako Oguma, Takuya Sawabe  
Hiroshima Red Cross Hospital and Atomic-Bomb Survivors Hospital, Hiroshima, Japan

Conflict of interest: None

[Abstract] IgG4-related disease (IgG4RD) is a systemic chronic inflammatory disease characterized by high serum IgG4 level and tissues fibrosis and infiltration of IgG4-positive plasma cells. Here we report a case of IgG4RD presented with urinary tract obstruction alone. [Case] A 79 years old woman visited an orthopedic clinic because of left back pain. An MRI scan showed right hydronephrosis and she was consulted to our hospital. A CT scan demonstrated right urinary obstruction at the level of L5, which suggested ureteral cancer. Urine cytology tests were twice negative and renal scintigraphy showed no signal at right kidney. Cystoscopy showed neither inflamed nor malignant lesions at the obstructed ureter. A PET-CT scan showed only weak signal in the area. Her serum IgG4 was 340 mg/dl, however, there were no other lesions that suggested IgG4RD on imaging. We could not rule out ureteral cancer, hence, we performed right ureteronephrectomy. Postoperative pathohistologic examination revealed an infiltration of IgG4-positive cells, which is compatible with IgG4RD. [Conclusion] There are a few case reports of



IgG4RD that presented with urinary tract obstruction alone. Clinicians should be careful that urinary tract obstruction could be an only manifestation of IgG4RD.

### **P1-214**

#### **Clinical evaluation of 39 patients with adult onset Still's disease in our unit**

Hiroshi Kanazawa, Hiromitsu Takemori

Department of Rheumatology, Aomori Prefectural Hospital, Aomori, Japan

Conflict of interest: None

**Objectives:** To describe the onset, clinical features, treatment and prognosis of patients with adult onset Still's disease (AOSD). **Methods:** 39 patients with AOSD fulfilling Yamaguchi criteria between April 1984 and March 2014 were analyzed retrospectively. **Results:** Clinical findings were as follows (%): female (77), mean age at diagnosis (55), fever (100), arthralgia (80), typical rash (85), neutrophilic leukocytosis (85), sore throat (59), lymphadenopathy/ splenomegaly (26), elevated transaminase levels (82), negative RF/ANA (82), and elevated serum ferritin levels (92). Corticosteroid was used for all cases, and steroid pulse therapy for 6 cases. 15 cases (39%) were treated with methotrexate (MTX), and 9 cases (23%) with tacrolimus (TAC). Corticosteroid was stopped in 4 cases. Tocilizumab had to be added to control the disease that is refractory to TNF inhibitor, or MTX and TAC combination therapy. All treatment was stopped in 7 cases. Of 8 death cases (21%), pneumocystis pneumonia (PCP) developed at the time of consolidation therapy, or tapering of PSL in 6 cases. About the PCP onset, the characteristic clinical feature was not identified. **Conclusion:** The clinical course of AOSD is complicated, and it is necessary to be careful about PCP after the immunosuppressive therapy.

### **P1-215**

#### **A case of Pulmonary arterial hypertension(PAH) complicated by refractory Adult Onset Still's Disease**

Tomoaki Machiyama, Yuko Shirota, Kanae Akita, Kyohei Nakamura, Ryu Watanabe, Yoko Fujita, Hiroshi Fujii, Tomonori Ishii, Hidero Harigae  
Tohoku University Hospital

Conflict of interest: None

[Background] AOSD is an inflammatory disease of idiopathic origin and pathogenesis. Although interstitial pneumonia, pericarditis are commonly observed, PAH is extremely rare, and there are few previous reports. Here, we reported a case of recurrent AOSD complicating with PAH. [Case] In 1997, a 48-year-old woman had been diagnosed with AOSD based on the presence of fever, arthritis and erythema. In 2004, EBV-DNA levels elevated to 930 copy /ug in her blood. It was detected only in B cells without monoclonality, and not diagnosed as chronic active EBV infection. In 2005, echocardiography showed the evidence of right ventricular strain. In 2009, she was admitted to our hospital for evaluation of dyspnea. Right heart catheterization revealed a mean pulmonary-artery pressure of 38mmHg, diagnosed as PAH. Sildenafil, were initially administered. In 2013, additionally constitutive immunosuppressive therapy started as IVCY500mg/ month X 10 times. Right heart catheterization was evaluated in March, 2014, showing normalized mPAP20. [Conclusion] The medication of pulmonary vasodilatation and the constitutive immunosuppressive therapy were effective on PAH with AOSD. Although the relation between PAH and EBV was unknown, EBV was often detected during the clinical course.

### **P1-216**

#### **A case of adult-onset Still's disease presented with ileocecal ulcer**

Yoshiki Nagai, Naonori Tsuda, Kae Onishi, Takayasu Kise, Yuji Miyoshi, Satoshi Watanuki, Eigo Kikuchi, Takahiro Nunokawa, Toshioki Sawaki, Naoto Yokogawa, Kota Shimada, Shoji Sugii  
Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center

Conflict of interest: None

[Case] A 78-year-old female was admitted to our hospital because of arthralgia of wrists and shoulders and daily spiking fever in January 2014. We suspected adult-onset Still's disease (AOSD) because of rash on her neck and trunk, arthritis and elevation of liver function test and serum ferritin concentrations (5375mg/ml). We conducted investigations including blood cultures, transthoracic and transesophageal echocardiography, biopsies of axially lymph node, random skin, bilateral temporal artery and bone marrow, but all were negative. Colonoscopy showed circumferential ulcers in ileocecal region. We suspected tuberculous enteritis, but there were no findings which suggested tuberculosis. We started antituberculosis agents because FDG-PET/CT scan showed increased uptake in ileocecal lesions and we could not rule out tuberculous enteritis. However, she had persistent fever and developed right-sided pleural effusion. Prednisolone (PSL) was started because of less possibility of intestinal tuberculosis. After we started PSL, she developed defervescence. [Conclusion] Abdominal pain in AOSD patients may occur in 1-48% in previous research. In our case, ileocecal ulcer may be associated with AOSD because ileocecal ulcer improved in accordance with defervescence after treatment of AOSD.

### **P1-217**

#### **A case with refractory adult onset Still's disease, for which liposteroid was effective**

Naruhiko Takasawa, Yukio Sekiguchi, Takeshi Sasaki

Department of Internal Medicine, Department of Rheumatology, NTT East Tohoku Hospital, Sendai, Japan

Conflict of interest: None

A 30-year-old-woman had an episode of high fever, sore throat, skin rash and polyarthralgia. Laboratory examination showed WBC16780/ml, CRP12.53mg/dl, ALP230IU/l, GTP33IU/l, GOT30IU/l, GPT35IU/l, LDH254IU/l, ferritin662.5, and negative for anti-nuclear antibody and rheumatoid factor. She was diagnosed adult onset Still's disease and 60mg of prednisolone was administered daily. She was afebrile for several days. Since she had high fever again, steroid pulse therapy was performed, and then 80mg of prednisolone was administered daily. Nonetheless, she had still high fever, skin rash spread, liver dysfunction became worse and ferritin elevated to 19110. Though methotrexate was administered, her condition still got worse, and then dexamethasone palmitate was added. She became afebrile, her condition got better and steroid pulse therapy was performed twice. The numbers of WBC promptly got back within normal range. The levels of CRP and ferritin also became normal. Prednisolone was gradually reduced to 20mg/day, and then dexamethasone palmitate was reduced from every day to three times a week, twice a week, once a week, and discontinued. Without relapse, she was discharged from the hospital.

### **P1-218**

#### **A case of severe fever with thrombocytopenia syndrome mimicking adult-onset still disease**

Yushiro Endo<sup>1</sup>, Tomohiro Koga<sup>2</sup>, Atsushi Kawakami<sup>2</sup>

<sup>1</sup>Kamigoto Hospital, Nagasaki, Japan, <sup>2</sup>Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences

Conflict of interest: None

A 61-year-old man, who had previously been in good health, visited the hospital complaining fever, epigastric distress and diarrhea. He was referred to our hospital due to thrombocytopenia and admitted for further evaluation. Laboratory investigation showed that WBC: 1300/mL, Hb: 14.3g/dl, PLT 47000/mL, elevated AST, LDH, CPK, hypocalcemia, and hyperferritinemia. He had no evidence of arthritis or skin rash. PCR examination revealed severe fever with thrombocytopenia syndrome (SFTS). Accordingly, he was initiated methylprednisolone pulse therapy, recombinant thrombomodulin, plasmapheresis and ribavirin therapy and was successfully treated. Here we show a case of SFTS patient who was difficult in distinguishing with adult-onset still disease because the fever and hyperferritinemia had mainly appeared at time of first visit. We report clinical points of differences between these two diseases.

### P1-219

#### The clinical characteristics in patients with adult-onset Still's disease (AOSD) treated with biologics

Hisae Ichida, Yasushi Kawaguchi, Mari Tochihara, Hidenaga Kawasumi, Yuko Okamoto, Masanori Hanaoka, Sayumi Baba, Akiko Tochimoto, Yasuhiro Katsumata, Kae Takagi, Hisashi Yamanaka  
Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: None

[Objectives] Adult-onset Still's disease (AOSD) is an acute inflammatory disorder of unknown origin. It is well known that a number of patients with AOSD have RA-like clinical courses. In the present study, we examined the clinical characteristics in patients with AOSD treated with biologics. [Methods] Ninety patients with AOSD who were treated in Institute of Rheumatology, Tokyo Women's Medical University enrolled in this study. The patients group consisted of 30 men and 60 women. We classified the patients with AOSD into 2 groups; RA-subtype (n = 20) who met the revised criteria of American College of Rheumatology clinical diagnostic criteria for RA and nonRA-subtype (n = 70) who didn't meet it. [Results] One patient in nonRA-subtype used TCZ, IL-1Ra. TCZ had good efficacy of in refractory AOSD with systemic symptoms. In RA-subtype AOSD, 6 patients used biologics (IFX, ETN, ADA, TCZ). There was no difference in CRP, serum ferritin, serum IL-18 in onset age, sex between biologics use group and non-use group. The PIP joint narrowing and osteosclerosis and atlantoaxial subluxation were more frequent in biologics use group than in non-use group. Tocilizumab were used to five patients in RA-subtype AOSD. It had efficacy on both systemic and articular symptoms.

### P1-220

#### Severe Adult Onset Still Disease treated with tofacitinib: a case report

Kazuhiro Hamasato, Shinpei Oonari, Satoshi Kawaai, Taiga Ikezawa, Ryuta Endo, Hirotochi Matsumoto, Shigekazu Takahashi, Norihiko Watanabe, Yasushi Nawata  
Saiseikai Narashino Hospital, Chiba, Japan

Conflict of interest: None

The clinical efficacy of plasma exchange (PE) and tocilizumab (TCZ) in patients with Adult onset still disease (AOSD) has been reported in several studies. Here we present a refractory case of AOSD treated with tofacitinib. [case report] A 55-year-old male patient suffered from remittent fever, sore throat and arthralgia was diagnosed with AOSD and was treated with corticosteroid pulse therapy followed by oral prednisolone (50mg/day) and PE and CHDF. But the patient was refractory to previous therapy, and additional treatment of TCZ enabled leaves him from PE. When the dose of prednisolone was decreased to 22.5mg/day, disease flare occurred. He was re-treated with corticosteroid pulse therapy, PE, and TCZ, but disease activity persisted. After obtaining the informed consent, we substituted Tofacitinib (10mg/day) for TCZ. Since Tofacitinib treatment was partially effective, combination therapy with Tofacitinib (20mg/day) and TCZ was carried out eventually, and then he could leave hospital. [conclusion] We speculated that suppression of various proinflammatory cytokine such as interleukin-6 is effective to a treatment for AOSD. In this patient, Tofacitinib showed measureable efficacy to AOSD. We estimate that Tofacitinib will be one of the treatment options for AOSD.

### P1-221

#### A case of adult onset Still disease which was triggered by drug eruption

Sachiko Fukumi, Keiichiro Matsunaga  
Department of Internal Medicine, Yokosuka General Hospital Uwamachi

Conflict of interest: None

A 72-year old woman with past history of SLE was observed only. She was admitted to the former hospital because of urinary tract infection. She was getting better with antibiotic treatment, but rash appeared and spread rapidly despite withdrawal of antibiotics. On the 14th hospital

day, she transferred at our hospital. She had fever, rash, lymphadenopathy, liver damage and hyper coagulopathy, so we diagnosed with drug-induced erythroderma and treated with prednisolone. Although she had myocarditis and atypical lymphocytes, she was improved. Two months later, she was hospitalized with pneumonia and urinary tract infection. After 2-week antibiotic treatment, she was discharged, but she had high ferritin level and recurrent rash during hospitalization. One month later, she had the third admission because of arthralgia and fever. She showed fever, arthralgia, leukocytosis and liver damage, so we diagnosed with adult onset Still disease. After methylprednisolone pulse treatment subsequent taking methotrexate, she was improved. We checked HHV6 IgG titer on admission day and 28<sup>th</sup> day after discharge on first admission, there was eight times difference between those days. We learned reactivation of HHV6 from this case, which was a potential cause of adult onset Still disease.

### P1-222

#### Successful tocilizumab treatment in a patient of adult-onset Still's disease with the history of HBV infection

Akiko Suzuki, Nobuaki Yamauchi, Yasuhiro Hakamata  
Shizuoka General Hospital, Shizuoka, Japan

Conflict of interest: None

[Objectives] Recent advances of biologic agents allow us to treat the patient with refractory Adult onset Still's disease (AOSD). We are always concerned about the HBV reactivation, when considering about hepatitis B virus (HBV) infection. We report the successful treatment for refractory AOSD with a history of HBV, using Tocilizumab (TCZ). [Case] The patient was a 69-year-old female. She developed pyrexia, pruritic rash in the trunk and limbs, polyarthralgia and pharyngalgia, and had been prescribed NSAIDs without effectiveness for several weeks, and was referred to our hospital. The elevated WBC counts, liver enzymes and LDH and high serum ferritin level (3765 ng/ml) were compatible with AOSD based on the Yamaguchi's criteria as well as HBs antigen negative and HBc antibody positive. After the therapy of prednisolone (PSL 30 mg/day), her systemic symptoms relapsed 2 weeks later. Serum ferritin level elevated to 14413 ng/ml. TCZ (162 mg/ every 2 weeks s.c.) was administered on the day 32<sup>th</sup>, resulted in improvement of liver enzymes, LDH level and serum ferritin level (< 150 ng/ml). [Conclusion] We report here a case of AOSD with the high risk of HBV reactivation. We conclude that TCZ is an available therapeutic option for the treatment of refractory AOSD with high risk of HBV.

### P1-223

#### An increased serum IL-18 level was ascertained, after remission in a case of clinically atypical AOSD

Mika Kobuna, Yoko Miura, Rika Okada, Masanobu Horikoshi, Shoko Kobayashi, Shigeo Inokuma  
Department of Allergy and Rheumatic Diseases, Japanese Red Cross Medical Center, Tokyo, Japan

Conflict of interest: None

Case: A 41-year-old man was admitted to our hospital because of spike fever and arthralgia. In 2011, membranoproliferative glomerulonephritis was diagnosed in kidney biopsy and treated with PSL5mg+CyA50mg+MZR25mg/day after the initial therapy. Pharyngalgia and spike fever developed, followed by bilateral severe gonalgia several days later, and he could hardly walk. He was hospitalized in nephrology department, antibiotic (MEPM+VCM) did not work, fever and arthralgia sustained, and he got enrolled to our department. Serum ferritin level was 6760 ng/mL, but liver enzyme levels increased only slightly afterward. Slight skin lesion developed only transiently. Suspected diagnosis was Adult-onset Still disease (AOSD), as symptoms and signs barely met Yamaguchi's criteria. After NSAIDs partially cured his arthralgia, 20 mg of PSL was started. He fully took a turn for the better. It was revealed that serum IL-18 level at the time before NSAID started had been 88700 pg/mL, and decreased after administration of PSL. Discussion: Serum IL-18 level increase would be an important and useful marker, which could indicate a disease that might be close to AOSD.

### P1-224

#### Refractory adult onset still's disease following hypersensitivity to TMP/SMX and bisphosphonate under treatment with tocilizumab

Yasuhiro Suyama, Kiyofumi Hagiwara

JR Tokyo General Hospital, division of Rheumatology

Conflict of interest: None

We report here a refractory adult onset still's disease following drug hypersensitivity reactions under the treatment with tocilizumab. A 48-year-old female, with known AOSD for 5 years, was admitted to our hospital with a history of spiking high fever, skin rash, and arthralgia. Her symptoms were refractory to the initial treatment with prednisolone and *tocilizumab* was added. However, the patient was diagnosed with *pneumocystis carinii pneumonia* during this induction therapy. Ten days after the initiation of TMP/SMX, the patient developed fever and skin rash with the worsening of adult onset still's disease. The exacerbation was successfully treated after the higher dose of prednisolone (100mg/day) and the resuming tocilizumab. Although the patient finally discharged home with prednisolone 8mg/day, readmitted was required in one month. This flare was triggered by drug hypersensitivity reaction to bisphosphonate, because, her worsened condition was developed 7 days after the prescription at outpatient clinic, which had been postponed for the possibility of the elevation of liver function test during the previous admission. Our case illustrates that disease flare could be triggered by both new agent and medications which has previously been prescribed without any side effects.

### P1-225

#### Prognosis and need of VP-16 in autoimmune-associated hemophagocytic syndrome

Yuri Nakamura, Rintaro Saito, Yoshie Gon, Takumi Nagamoto, Hiroataka Yamada, Kenta Misaki, Toshihiko Yokota  
Kurashiki Central Hospital

Conflict of interest: None

[Objectives] To estimate prognosis and necessity of VP-16 in Hemophagocytic syndrome (HPS). [Methods] Seventeen patients admitted to our hospital and diagnosed as HPS were enrolled. The age when diagnosed, peripheral blood cell count, serological marker such as CRP, LDH, ferritin, D-dimer and fibrinogen were examined. The outcomes and the use of VP-16 were compared. [Results] The base line of the diseases were followed; adult onset Still's disease in 9, systemic lupus erythematosus in 6, rheumatoid arthritis (RA) with vasculitis in 1 and RA in 1. Fifteen survived and two died. Fourteen needed immunosuppressive agents besides corticosteroid, and five needed VP-16 therapy. Median starting dosage of prednisolone was  $0.89 \pm 0.04$  mg/kg/day. In the dead cases, the average age was higher ( $82.5 \pm 1.5$  y.o. vs  $51.6 \pm 5.0$  y.o.:  $p=0.043$ ). And those used VP-16 showed higher value of CRP ( $6.00$  mg/dL vs  $14.52$  mg/dL  $p=0.021$ ) and higher platelet count when the treatments started ( $23.8 \pm 2.0 \times 10^4/\mu\text{L}$  vs  $10.4 \pm 1.6 \times 10^4/\mu\text{L}$ :  $p=0.024$ ). As for serum ferritin, LDH, D-dimer and Fib, there were no significant difference in this study. [Conclusion] Age can be a prognosis factor in HPS. Serum CRP level is useful in predicting whether VP-16 therapy is needed.

### P1-226

#### A case of CD4+CD8+ T-cell large granular lymphocyte leukemia exhibiting Felty's syndrome

Akihiko Nakabayashi, Yoshinori Katada, Yuta Yamaguchi, Sara Murakami, Madoka Morimoto, Kazushi Konma  
Sakai City Hospital Organization Kidney, Metabolism and Immunity, Osaka, Japan

Conflict of interest: None

[Case] A 78 year-old female was admitted to our hospital. As pancytopenia developed seven months before admission, she was diagnosed as myelodysplastic syndrome by a hematologist. Two months before admission, she had polyarthritis. Both of RF and ACPA were positive, fulfilling the 2010 ACR/EULAR rheumatoid arthritis classification criteria. Two

days before admission, she had strong epigastralgia. After admission, splenomegaly was noted by computer tomography, suggesting she had Felty's syndrome considering that she had rheumatoid arthritis (RA) and leukocytopenia. Among the peripheral blood lymphocytes, 28.7% were CD4+, CD8+ double positive T lymphocytes, while 20.0% of lymphocytes in the bone marrow were CD3+, CD4+, CD5+, CD8+, CD56-, TCR $\alpha\beta$ +. T-cell receptor gene rearrangement was detected both in the peripheral blood and in the bone marrow, making the diagnosis of mature T-cell neoplasms. [Discussion] There have been a few reports describing the association of RA with mature T-cell neoplasms such as T-cell large granular lymphocytic leukemia (T-LGL). Although we found few azurophil granules in the abnormal T lymphocytes in this case, the disease was similar to T-LGL in clinical settings. Some patients with Felty's syndrome can be with mature T-cell neoplasms such as T-LGL.

### P1-227

#### Therapeutic effects of the biological preparations in Spondyloarthritis (SpA)

Hiroki Yabe, Chihiro Terai

Division of Rheumatology, Jichi Medical University Saitama Medical Center

Conflict of interest: None

[Objectives] Spondyloarthritis (SpA) is a group of chronic inflammatory rheumatic disease including AS and PsA. We investigated the therapeutic effects of the biological preparations (Bio) in patients with SpA. [Methods] In 2007-2014, 37 patients were diagnosed with SpA and nine (24%) of which were treated with Bio. Efficacy was evaluated using patients' pain VAS, DAS28, BASDAI, and inflammatory markers. [Results] Nine patients with PsA, 2 with AS, and 2 with SAPHO syndrome were included in this study. ADA was used in 6 patients and IFX in 3 patients. Bio was started at 22-68 years old (yo) (avg. 49.2). The follow-up period was average 30 mo (14-53). In PsA, average DAS28-CRP was decreased from 3.5 to 1.6 in the last follow-up, and dermatitis was improved or diminished in all cases. Two patients with AS showed markedly improved BASDAI. In 2 refractory cases with severe SAPHO, ADA was tried. In early stage, pain VAS was markedly decreased. One case stopped ADA after 1.5 yr. at her request, another one stopped after 2 yr. because of paradoxical rash in eyelid. After stopping ADA, pain relief was continued in both cases. [Conclusion] Recently, Bio became usable to AS and PsA in our country. Our study showed good therapeutic effects of Bio in the patients with SpA.

### P1-228

#### A case of elderly-onset axial spondyloarthritis successfully treated by abatacept

Yoshitaka Kumon, Shigeru Nojima

Department of Rheumatology, Chikamori Hospital, Kochi, Japan

Conflict of interest: None

75 years-old woman suffering from fever, lumbago, truncal and limbs pain, and headache for two weeks, was referred to our hospital. She could not get up because of the shoulder- and hip-girdle pain on admission. Laboratory findings revealed CRP 18.7 mg/dl, ESR 108 mm/h, and negative for RF and ACPA. The administration of prednisolone (PSL) 10 mg/day suspicious of polymyalgia rheumatica (PMR) was started, however, the patient was consulted to our department because the symptoms remained. In physical findings, arthritis was observed in the hands, elbows, knees and shoulders, which was also confirmed by the ultrasonography and Ga scintigraphy. MRI and FDG-PET/CT revealed sacroiliitis and axial spondyloarthritis (SpA) was finally diagnosed. After starting MTX pulse therapy the patients improved to some extents, but it was difficult to control arthritis by decreasing in dose of PSL. After adding abatacept, arthritis activity had been decreased in remission, finally resulting in lumbago free despite of no PSL nor MTX administration. We encounter the aged SpA patients in clinical practice. Abatacept sometimes seems effective for SpA patients and we report some considerations about these conditions.

### P1-229

#### Analysis of tuberculous patients in the treatment of RA in Toneyama Hospital

Hiroyuki Nakaya, Koichiro Takahi, Kazuhiko Imoto  
National Hospital Organization, Toneyama Hospital

Conflict of interest: None

[Objectives] Most RA patients are compromised due to immunosuppressive effect of DMARD. Mycobacterium infection such as tuberculosis is one of serious problems. We clarify clinical characteristic of tuberculosis in the treatment of RA. [Methods] We extracted RA patients among tuberculosis patients sent to our hospital from 2008 Jan to 2014 Sep, and examined diagnostic method, type and severity of infection, RA disease activity, severity of tuberculosis and mortality. In order to clarify clinical characteristics and risk factors, correlation between these clinical data and RA background or therapeutic treatment were investigated. [Results] Thirty three (14 male and 19 female) were included and mean age was 68.2 years old. Expectoration smear was positive in 79% and it took 5.8 weeks until laboratory culture turns negative. We found them 12% high mortality rate, while diabetic myelitis affected mortality. Contents of prescription was steroid in 76%(mean dose was 6.2mg: 0-20mg), MTX in 39%, biologic DMARD in 12% in RA patients. Mean DAS 28-CRP 3.93 (3.07-4.74) indicated insufficient disease control of RA. [Conclusion] They were characterized as high rate of steroid prescription and mortality.

### P1-230

#### Comparison of specificities between two interferon-gamma release assays in RA patients

Takaki Nojima<sup>1,2</sup>

<sup>1</sup>Nojima Internal Medicine Clinic, <sup>2</sup>Department of Clinical Immunology and Rheumatology, Hiroshima University Hospital

Conflict of interest: None

[Purpose] To compare QuantiFERON-TB Gold In-Tube test (QFT-G) and T-SPOT. TB (TSPOT) for the detection of latent tuberculosis infection among patients with RA. [Method] Two interferon-gamma release assays (IGRA) test data and clinical information on 56 RA patients (51 female, average age 67.2) were collected. [Result] QFT-G was positive in 2 (3.6%) and indeterminate in 12 (21.4%). TSPOT was positive in 4 (7.1%) and indeterminate in 3 (5.4%). One of two QFT-G positive patients was also TSPOT positive. Five patients with IGRA positive (average age 83.7) had no evidence of active MTB disease. Among twelve QFT-G indeterminate patients, all showed low levels of IFN $\gamma$  in the mitogen well (positive control). The patient with low level of positive control and high level of negative control was rheumatoid vasculitis. QFT-G indeterminate patients were lower lymphocyte counts than the other RA patients (1141 vs 1543) and elder than the others (70.5 vs 66.3). [Discussion] In elder RA patients with low lymphocyte, TSPOT test is recommended rather than QFT-G.

### P1-231

#### A case of rheumatoid arthritis with multifocal skeletal tuberculosis during the treatment with methotrexate

Yoshikazu Fujikawa, Yuzuru Yamamoto, Yumiko Nobuhara, Takashi Nakazawa  
Osaka Saiseikai Nakatsu Hospital

Conflict of interest: None

The patient is a 56 year-old woman. She had an onset of rheumatoid arthritis (RA) 10 years ago. 4 months ago, we had treated her with methotrexate (MTX) 10mg. At the same time she complained of a swollen right inguinal lesion. Computed tomography (CT) showed enlargement of right supraclavicular, abdominal para-aortic, bilateral iliac arterial and right inguinal lymph nodes. We stopped MTX in a suspicion of malignant lymphoma or MTX-associated lymphoproliferative disorder. We underwent biopsy by right inguinal lymph nodes. The histological finding showed granulomas with caseous necrosis. <sup>18</sup>F-FDG PET revealed the lesions of cranial bone, sternal bone and left lower leg, so she admitted to

clarify the differential diagnosis including tuberculosis. The sputum culture and gastric juice was negative. The colonoscopic finding showed no enteric tuberculosis. A biopsy of extra-nodal lesions was rejected. By the positive result of IGRA-Tspot assay, extra-nodal lesions and the histopathology from lymph node we made a diagnosis of multifocal skeletal tuberculosis. We started to treat with 4 drugs combination therapy. The CT showed the partial improvement at 2 months later. We advocate the importance to the differential diagnosis of the multiple lymphadenopathies in MTX treated RA patients.

### P1-232

#### Two cases of end-stage lupus nephritis patients complicated with pleuritis by non-tuberculous mycobacterial infection (NTM)

Yasuhiko Yoshinaga<sup>1</sup>, Manabu Tsuno<sup>2</sup>, Keiji Ohashi<sup>2</sup>, Tetsushi Aita<sup>1</sup>, Susumu Nishiyama<sup>1</sup>, Shoji Miyawaki<sup>1</sup>

<sup>1</sup>Rheumatic Disease Center, Kurashiki Medical Center, Kurashiki, Japan,

<sup>2</sup>Okayama University Graduate School of Medicine, Okayama, Japan

Conflict of interest: None

[Case1: 47 years old woman] She developed SLE with fever and pleurisy at 24 years old, and had repeated the nephrotic syndrome since 30 years old, gradually renal failure worsened, was introduced hemodialysis at 43 years of age. She was admitted because of fever, right chest pain, cough and, the elevation of CRP. She was diagnosed with pleurisy by *M.avium*, because *M.avium*-PCR in her pleural effusion revealed positive. Her pleurisy was recovered by the treatment with RFP 450mg, CAM 200mg/day and EB 250mg/after dialysis. Antibacterial agents were administered continuously for one year. [Case2: 60 years old woman] She developed SLE with fever and pleurisy at 24 years old, and had repeated the nephrotic syndrome since 30 years old, gradually renal failure worsened, was introduced hemodialysis at 43 years of age. She was admitted because of fever, right chest pain, cough and, the elevation of CRP. She was diagnosed with pleurisy by *M.avium*, because *M.avium*-PCR in her pleural effusion revealed positive. Her pleurisy was recovered by the treatment with RFP 450mg, CAM 200mg/day and EB 250mg/after dialysis. Antibacterial agents were administered continuously for one year. [Conclusion] NTM is one of the cause of pleurisy of the lupus nephritis patients undergoing hemodialysis.

### P1-233

#### The review of the eight patients with pneumocystis pneumonia in our department

Takuya Hirai<sup>1</sup>, Kana Tanji<sup>1</sup>, Keigo Ikeda<sup>1</sup>, Shinji Morimoto<sup>1</sup>, Yoshinari Takasaki<sup>2</sup>, Iwao Sekigawa<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Juntendo University Urayasu Hospital, Chiba, Japan, <sup>2</sup>Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objective] We reviewed the characteristics and the datum of the patient with pneumocystis pneumonia (PCP) in our department. [Methods] We examined the eight patients of PCP treated in our department from 2010 to 2014. The diagnosis of the PCP was decided by the ground-glass opacity of both lungs in CT scan, and PCR positivity with the sputum/the broncho-alveolar lavage fluid, or beta-D-glucan positivity with blood. [Results] The patients were the average of 72.6 years old. The five were rheumatoid arthritis, and the others were different rheumatic disease (a patient of each SLE, polymyalgia rheumatica and microscopic polyangiitis). The six had taken steroids. The three had taken MTX. The three were using the biologics (one etanercept, two abatacept). The disease duration was from two months to 20 years. The beta-D-glucan mean was 903.9 pg/ml. The three were improved, the three were exitus, and the two have been treated. [Conclusion] Most of our PCP cases indicated old ages and the use of steroid. Additionally, the disease duration showed the tendency of being long. On the other hand, a case showed to develop PCP in two months after the start of treatment. The preventive therapy should be performed by means possible in the case with the high risk of PCP.

### P1-234

#### **A case of severe thrombocytopenia during treatment of pneumocystis pneumonia in a patient with rheumatoid arthritis**

Tetsushi Aita, Susumu Nishiyama, Yasuhiko Yoshinaga, Shoji Miyawaki  
Rheumatic Disease Center, Kurashiki Medical Center

Conflict of interest: None

Drug-induced immune thrombocytopenia (DITP) is usually caused by drug-induced antibodies that produce platelet clearance by the reticuloendothelial system. Although DITP is uncommon, it can have devastating, even fatal consequences associated with severe bleeding complications. It is therefore important that clinicians have a general understanding of this condition and the drugs that can cause it. A 78-year-old female had a slight fever, morning stiffness, and arthritis of wrists and knees in spring 2014. She was diagnosed with rheumatoid arthritis and steroid and methotrexate were prescribed. After a few months, she complained high fever and she was hospitalized on emergency. We diagnosed pneumocystis pneumonia because of diffuse ground glass opacity in chest CT and high levels of  $\beta$ -D glucan and trimethoprim-sulfamethoxazole (ST) was prescribed. ST was gradually tapered and was stopped on day 10 because of a drug eruption. On day 11 of treatment, her platelet count was 4,000/ $\mu$ l. Petechiae and ecchymoses, and buccal hemorrhage developed. A platelet transfusion and steroid pulse therapy given had little effect on the platelet count. We considered DITP and had followed up, and then sustained recovery occurred during the next few weeks.

### P1-235

#### **2 or 3 per week TMP/SMX would reduce the adverse events in patients with highly dose GC therapy**

Nao Oguro, Shinya Seki, Sho Ishii, Masayu Umemura, Takahiro Tokunaga, Ryo Takahashi, Kuninobu Wakabayashi, Yusuke Miwa, Tsuyoshi Kasama  
Division of Rheumatology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] TMP/SMX is used in prevention of *Pneumocystis pneumonia* (PCP). Despite its efficacy, adverse events can limit the use of TMP/SMX. We reviewed the rate and types of adverse events due to TMP/SMX dose. [Methods] 81 patients with highly dose GC therapy for the first time in January 2012~September 2014 who were diagnosed as collagen disease, were enrolled from our hospital. We compared group A (n=51, 7 tablets per week TMP/SMX) and group B (n=30, 2 or 3 tablets per week TMP/SMX), and examined the rate and types (rash, cytopenia, liver damage, renal damage, hyponatremia) of adverse events during the duration of hospitalization. [Results] The rate of adverse events was 30 % (24/81). The rate of adverse events in group A and group B were 41 % (24/51) and 10 % (3/30), respectively. The rate of adverse events in group B was significantly lower than in group A ( $p=0.002$ ). There were no significant differences in each adverse events, however there was a high tendency in group A. The continuation rate of TMP/SMX in group A and group B were 78% and 96%, respectively. There was no PCP in all patients during duration of hospitalization. [Conclusion] Group B would reduce the adverse events compared to group A in patients with highly dose GC therapy, and enable to continue the prophylaxis.

### P1-236

#### **A case of the Eosinophilic Granulomatosis with Polyangitis that de novo hepatitis B developed, and recovered by tenofovir disoproxil fumarate and entecavir**

Aihiro Yamamoto, Aiko Tominaga, Risa Sagawa, Takashi Kida, Amane Nakabayashi, Kazuki Fujioka, Yuji Kukida, Wataru Fujii, Ken Murakami, Takahiro Seno, Masataka Kohno, Yutaka Kawahito  
Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: None

[Case] A 60-year-old woman [Present history] Eosinophilic Granulomatosis with Polyangitis (EGPA) was developed at the age of 39, and

induction of remission and long-term maintenance were obtained by prednisolone (PSL). Meanwhile, we often recommended nucleoside analogue treatment to her because the quantity of HBV-DNA was always 5-6 LOG copies/ml, but I could not receive her consent at the time. EGPA was exacerbated on May, 2014, and then, PSL dosage was increased from 4 mg/day to 30 mg/day. AST, ALT, and the quantity of HBV-DNA increased in June when PSL dosage was reduced to 15mg/day in July. Then, AST and ALT rose to 1,054 U/L and 680 U/L, respectively and the quantity of HBV-DNA increased to 8.4 LOG copies/ml in September. [Progress] The administration of tenofovir disoproxil fumarate (TDF) 300 mg/day started after hospitalization, but the examination report did not show apparent improvement, so that PSL 30 mg/day and 0.5 mg/day of entecavir were added on the 6th and 19th day, respectively. And afterwards, AST and ALT decreased to two digits on the 42nd day, and the quantity of HBV-DNA decreased to 5.1 LOG copies/ml. [Conclusion] It is necessary to provide early nucleoside analogue treatment for cases that the quantity of HBV-DNA can be detected.

### P1-237

#### **A case of rheumatoid arthritis treated with abatacept combined with systemic lupus erythematosus and bronchiolitis obliterans**

Atsushi Kondo<sup>1</sup>, Shusaku Nakashima<sup>2</sup>, Hiroki Ozaki<sup>2</sup>, Shohei Kawakami<sup>1</sup>, Risa Wakiya<sup>2</sup>, Hiromi Shimada<sup>2</sup>, Yohei Takeuchi<sup>2</sup>, Miharuru Izumikawa<sup>2</sup>, Tomohiro Kameda<sup>2</sup>, Kentaro Susaki<sup>2</sup>, Hiroaki Dobashi<sup>2</sup>

<sup>1</sup>Postgraduate Clinical Education Center, Kagawa University Hospital, Kagawa, Japan, <sup>2</sup>Department of Internal Medicine, Division of Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University, Kagawa, Japan

Conflict of interest: None

Case: 69 years old, female. Clinical course: She had diagnosis as systemic lupus erythematosus (SLE) in 1983. She was treated with corticosteroid (CS) and cyclophosphamide (CPA). In 1999, she occurred with bronchiolitis obliterans (BO). And then, she repeated hospitalization because of asthma attack and pneumonitis. In June 2014, she had right wrist pain and swelling and admitted in our facility. She was treated with CS (5mg/day) without CPA on admission. Her laboratory data showed high titer of anti-cyclic citrullinated peptide antibody (ACPA) and no evidence of tuberculosis. Joint power Doppler ultrasonography and enhances magnetic resonance imaging (MRI) of right wrist revealed synovitis, erosion and bone marrow edema. We diagnosed as rheumatoid arthritis (RA) because of her arthritis, laboratory data and findings from clinical image. We considered that the treatment with methotrexate (MTX) was difficult because of her pulmonary disorder. We started treatment with abatacept because she had some poor prognostic factors. Discussion: We often experience a case to hesitate the selection of therapy for RA patients combined with BO. We report a treatment strategy including biologics for RA patients combined with pulmonary disorder and high risk of infection

### P1-238

#### **Hepatitis B infection in rheumatoid arthritis patients in our hospital**

Yasuaki Aoki<sup>1</sup>, Hidetoshi Kagawa<sup>2</sup>, Ryutarou Yamanaka<sup>2</sup>  
<sup>1</sup>Department of Orthopaedic Surgery, Japanese Red Cross Society Himeji Hospital, Himeji, Japan, <sup>2</sup>Department of Internal Medicine, Japanese Red Cross Society Himeji Hospital, Himeji, Japan

Conflict of interest: None

[Objectives] Japan College of Rheumatology and Japan Society of Hepatology proposed a guideline for HBV screening before starting immunosuppressive therapy for rheumatoid arthritis patients. We reported the results of HBV screening in rheumatoid arthritis patients treated in our hospital according to this guideline. [Methods] At first, HBsAg was tested. If HBsAg was negative, HBcAb and HBsAb were tested. When HBcAb and/or HBsAb were positive (resolved HBV infection), HBV-DNA level was quantified by real-time PCR. [Results] Two of 355 rheumatoid arthritis outpatients were vaccinated against HBV. Three were positive for HBsAg. These were diagnosed as inactive HBV carriers. For two of the three, entecavir was administered prophylactically. These three patients were treated by SASP and/or BUC. 79 resolved HBV infection patients were recognized. Three were positive for HBV-DNA (HBV reac-

tivation). For these three, entecavir was also administered and immunosuppressive therapies (Infliximab + MTX for one, and MTX for others) were continued. Active hepatitis B was not observed. [Conclusion] HBV reactivation was occurred in rheumatoid arthritis patients not only treated with biologics but also with csDMARDs. We must do HBV screening in rheumatoid arthritis patients before starting therapy.

### P1-239

#### Examination of background for cytomegalovirus reactivation

Takahiro Tokunaga, Masayu Umemura, Shinya Seki, Nao Oguro, Mayu Saito, Sakiko Isojima, Ryo Takahashi, Kuninobu Wakabayashi, Tsuyoshi Kasama

Division of Rheumatology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] In immunosuppressive therapy in collagen diseases, CMV reactivation occurs frequently. We examined the background for CMV reactivation under treatment with PSL. [Methods] We examined CMV antigen positive rate in patients who received first time more than PSL 0.3mg/kg/day or mPSL pulse therapy in 2012-2014. The observation period was set to the start date to treat 10 week, age, gender, PSL initial dose, the presence of mPSL pulse therapy and immunosuppressant. It had been decided that CMV reactivation was one or more positive cells in the second slide at the C10/C11 method. [Results] 100 patients were observed (43 vasculitis, 11 PM, 9 DM, 18 SLE, 4 AOSD, 3 SSc, 2 BD and others 10 cases) who were treated first time. We showed CMV reactivation was 22 cases (8 vasculitis, 4 PM, 4 DM, 5 SLE, 0 AOSD, 0 SSc, 1 BD). There were significant differences between PSL initial dose, the presence of mPSL pulse therapy ( $p < 0.05$ ), furthermore combination therapy with PSL and immunosuppressant were tends to increase the risk. Immunosuppressant combination was at risk of CMV reactivation ( $p < 0.05$ ). There were no difference between age, gender. [Conclusion] CMV reactivation is likely to occurs by further suppress an immune and may be suggest that difference depending primary disease.

### P1-240

#### Study of serum procalcitonin level in collagen disease patients in our department

Kenji Sakai<sup>1</sup>, Tetsu Itami<sup>1</sup>, Asuka Inoue<sup>1</sup>, Chiemi Tasaki<sup>1</sup>, Shinkai Ri<sup>1</sup>, Taeko Yumoto<sup>2</sup>, Toshihiko Shiga<sup>1</sup>, Kayo Asato<sup>1</sup>, Tomohiro Yano<sup>1</sup>, Shoichi Hino<sup>1</sup>, Kazuya Kishimoto<sup>1</sup>, Hideki Shimazu<sup>2</sup>, Yasuaki Nagare<sup>1</sup>, Yuji Nozaki<sup>1</sup>, Koji Kinoshita<sup>2</sup>, Masanori Funauchi<sup>1</sup>, Itaru Matsumura<sup>1</sup>

<sup>1</sup>Kinki University Faculty of Medicine, <sup>2</sup>Sakai Hospital Kinki University Faculty Medicine

Conflict of interest: None

[Objectives] In the patients with connective tissue diseases, it may be difficult to discriminate exacerbation from other pathologies when they are febrile and inflammatory responses are highly positive. Here serum procalcitonin (PCT) level was evaluated in the patient with connective tissue disease. [Methods] We analyzed 46 patients with adult-onset Still's disease (AOSD) or systemic lupus erythematosus (SLE) or ANCA-associated vasculitis (AAV) who became hospitalized accompanied by systemic inflammatory response syndrome (SIRS). Patients were included 13 AOSD, 20 SLE and 13 AAV. Patients who were suspected to have bacterial infections judged from various culture tests and improvement by antibiotics were classified into bacterial-infection group (A), and others were classified into non bacterial-infection group (B). [Results] 9 patients belonged to group A and 37 patients to group B. PCT was higher significantly in group A. Among the group B patients, serum PCT levels in 34 patients were lower than 0.5 ng/ml. There was no difference in the PCT levels of each diseases among 32 patients with connective tissue diseases which onset or flare. [Conclusion] Measure of serum PCT was thought useful also in the patients with connective tissue diseases to assess the bacterial infection.

### P1-241

#### Comparison of neutrophil CD64 and procalcitonin as an infection marker in patients with rheumatoid arthritis

Toshihiro Matsui<sup>1</sup>, Akiko Komiyama<sup>2</sup>, Koichiro Horie<sup>1</sup>, Hidefumi Fukuda<sup>1</sup>, Kanako Iwata<sup>2</sup>, Hirotaka Tsuno<sup>1</sup>, Hideki Ogihara<sup>1</sup>, Misato Kawakami<sup>1</sup>, Atsushi Hashimoto<sup>1</sup>, Shigeto Tohma<sup>2</sup>

<sup>1</sup>Department of Rheumatology, Sagamihara National Hospital, National Hospital Organization, <sup>2</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, National Hospital Organization

Conflict of interest: None

[Objectives] To compare the utility as an infection marker between neutrophil CD64 and procalcitonin (PCT) in patients with rheumatoid arthritis (RA). [Methods] Neutrophil CD64 and PCT were measured in 61 RA patients complicated with infection whose pathogens were proven. Cut-off value was 2000 molecules/cell for CD64 and 0.5 ng/ml for PCT, respectively. Steroid was used in 57 patients (47.5%), and Biologics in 17 patients (27.9%). [Results] Sensitivity of CD64 and of PCT was 91.8% and 47.5%, respectively. Sensitivity of CD64/PCT by pathogens was as follows; mycobacteria (n=4): 75%/0%, gram-positive bacteria (n=16): 87.5%/37.5%, gram-negative bacteria (n=31): 93.5%/67.7%, viruses (n=4): 100%/0%, fungi (n=1): 100%/100%, and pneumocystis jiroveci (n=5): 100%/20%. This utility was confirmed even in patients using biologics including tocilizumab. In death cases (n=7) by bacteria infection, sensitivity of CD64/PCT was 100%/71.4%, respectively. [Conclusion] CD64 was superior to PCT in detection of a variety of infections. Combination of CD64 with PCT may be useful to differentiate the pathogens or to evaluate the severity of infection in RA patients.

### P1-242

#### A challenging case of cryptococcal meningoencephalitis with various neurological symptoms in a patient with systemic lupus erythematosus to distinguish from neuropsychiatric lupus

Shigeto Horita, Hiroshi Fujii, Kiyooki Ito, Takeshi Zoshima, Hiromi Nuka, Satoshi Hara, Motohiko Aizu, Ryoko Hamano, Kazunori Yamada, Mitsuhiro Kawano

Division of Rheumatology, Department of Internal Medicine, Kanazawa University Hospital, Kanazawa, Japan

Conflict of interest: None

[Case] A 39 year-old woman with SLE presenting cryptococcal meningoencephalitis (CME). A year before admission, she was diagnosed with lupus nephritis (ISN/RPS class IV) and underwent combination therapy of prednisolone and tacrolimus. Two months before admission, she had intermittent fever and headache. Blood tests showed mild elevation of serum CRP to 1.0mg/dl. A week before admission, she had transient double vision and ptosis in the morning, but the symptoms disappeared in the afternoon. As the symptoms became to persist and she felt nausea and instability in walking, she was admitted to our hospital. Serum antibodies to double-stranded DNA and hypocomplementemia was within normal range and SLEDAI was 4. The number of CD4 positive lymphocyte decreased to 150/ $\mu$ l. Diffusion weighted MRI showed high intensity in the brainstem area, which were hard to distinguish neuropsychiatric SLE (NP-SLE). As NP-SLE or CME was suspected, cerebrospinal fluid (CSF) was drawn and india ink staining of CSF made diagnosis of CME. She was treated with antifungal agents and symptoms gradually disappeared. [Conclusion] This case indicates the difficulty to distinguish NP-SLE and CME according to the history and image findings. CME should be a differential diagnosis when to consider NP-SLE.

### P1-243

#### Necrotizing fasciitis by *Candida albicans* and subsequent fungemia by *Candida glabrata* in a patient with systemic lupus erythematosus

Kanae Akita, Tomoaki Machiyama, Kyohei Nakamura, Yoko Fujita, Yuko Shirota, Hiroshi Fujii, Tomonori Ishii, Hideo Harigae

Department of Hematology and Rheumatology, Tohoku University Graduate School of Medicine, Miyagi, Japan

Conflict of interest: None

A 65-year-old woman with a 2-year history of systemic lupus erythematosus (SLE) who received treatment with prednisolone (15 mg/day) and tacrolimus (2 mg/day) in combination with abatacept (a 500mg dose once every four weeks) was admitted for exacerbation of peripheral neuropathy in July 2014. She was treated with methylprednisolone pulse therapy and plasma exchange. Peripheral neuropathy was not improved and the limbs were swollen. Purulence was noted on the limbs and culture of the purulent was positive for *Candida albicans* (*C. albicans*). Liposomal amphotericin B (L-AMB, 200 mg/day) was initiated and subsequent debridement revealed necrotizing fasciitis by *C. albicans*. She underwent amputation of the left upper limb after the second debridement. We changed from L-AMB to fosfluconazole (F-FLCZ, 200 mg/day) 20 days after the amputation because the cultures of blood and the surgical wound site were negative for fungus. Six days after starting F-FLCZ, the blood culture turned out positive for *C. glabrata*. We assumed that fungemia by *C. glabrata* broke out due to use of F-FLCZ. Micafungin (150 mg/day) and L-AMB were administered to treat the fungemia. We reported a rare case of necrotizing fasciitis by *C. albicans* and subsequent fungemia by *C. glabrata*.

### P1-244

#### Clinical epidemiology of blood stream infection in rheumatic diseases in Japan

Masanori Hanaoka, Takahisa Gono, Yasuhiro Katsumata, Yasushi Kawaguchi, Hisae Ichida, Eiichi Tanaka, Hisashi Yamanaka  
Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: None

[Objectives] To clarify the clinical epidemiology of blood stream infection among patients with autoimmune disease including rheumatoid arthritis. [Methods] All episodes of positive blood culture in patients who admit to our institute were evaluated from April 2010 to January 2014. For culture-positive cases, clinical manifestations, underlying diseases, immunosuppressive agents (ISA) used, dose of steroid, persistent bacteremia and clinical outcomes were analyzed and compared between RA and non-RA subset. Persistent bacteremia was defined as at least two positive blood cultures for same organism obtained on different calendar days. [Results] During study period, 1064 sets of blood culture were performed. 78 sets of blood culture (0.14%) from 47 patients were positive. Culture-positive rate was 4.4% in RA, 3.4% in SLE and 6.4% in vasculitis. No significant differentiations were found in mortality in 30 days, prophylactic oral TMP-SMX, use of ISA and corticosteroid between two subsets. Persistent bacteremia was tend to be higher in non-RA subset. In multivariate analysis, dose of corticosteroid was higher ( $p < 0.01$ ) in non-RA subset. [Conclusion] In RA patients with bacteremia, dose of corticosteroid was lower but prognosis was similar compared with non-RA immunosuppressed patients.

### P1-245

#### Five cases of nocardiosis in patients with connective tissue disease

Takayasu Suzuka, Yoshihiro Hirai, Minako Hakamata, Hideyuki Shiba, Shuzo Yoshida, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa  
Department of Internal Medicine (I), Osaka Medical College

Conflict of interest: None

We reported 5 cases of nocardiosis in patients with connective tissue diseases (CTDs). 2 in rheumatoid arthritis (RA) with interstitial pneumonia, 1 in adult-onset Still's disease, and 1 in systemic lupus erythematosus with RA. The manifestation of nocardiosis were arthritis in 1 patient, brain abscess in 2, and pneumonia in 2. All patients were treated with corticosteroids and immunosuppressive drugs. They were administered meropenem or imipenem/cilastatin for the initiation therapy, and trimethoprim/sulfamethoxazole, or minocycline, or clarithromycin for the maintenance therapy. Subsequently, 3 patient cured, 1 died and 1 dropped out. In treatment of CTD, we have to note a risk of nocardiosis during long-term immunosuppressive therapy, and to pay attention for not only the pulmonary lesion but also the disseminated lesion.

### P1-246

#### A case of disseminated nocardiosis diagnosed early with microscopic polyangitis

Tomoki Miyoshi, Hideki Amuro, Nobuyasu Ishii, Toshiharu Sasaki, Minoru Shigesaka, Saki Tsujimoto, Akihiro Tanaka, Keiko Shimamoto, Tohru Nishizawa, Yonsu Son, Yoshio Ozaki, Tomoki Ito, Shosaku Nomura  
First Department of Internal Medicine, Kansai Medical University, Osaka, Japan

Conflict of interest: None

We report the case of a 74-year-old woman on hemodialysis who has been treated with corticosteroids for microscopic polyangitis in our hospital since July 2013. In December, she was admitted to our hospital because of fever on account of left knee pain for a week. Laboratory findings showed leukocytosis and CRP elevation. We punctured her left knee and obtained purulent synovial fluid. Gram positive and acid-fast filaments were observed in synovial fluid, and blood culture. The culture yielded a pure growth of Nocardia Sp, which was identified as *Nocardia farcinica* later on. Considering these findings, we diagnosed the patient with disseminated nocardiosis. We administered antibiotic therapy using imipenem/cilastatin and amikacin, and she was improved. Disseminated nocardiosis is opportunistic infectious disease and important complication for the patient with autoimmune disease by immunosuppressive agents. The diagnosis is based on the demonstration of organisms in culture. But cultures of Nocardia can take more than five days to grow. Therefore, the start of appropriate treatments can be delay. Such a delay can have dismal consequences. In our case, we considered that the administration of precise antibiotics by early diagnosis could contribute to ameliorate her condition.

### P1-247

#### A case report of SLE complicated with multiple nocardiosis

Tomoe Kaieda<sup>1</sup>, Hideo Ohtsubo<sup>1</sup>, Kenji Nakano<sup>2</sup>, Noriko Aoki<sup>1</sup>, Sanae Shigemizu<sup>1</sup>, Yoshiya Arishima<sup>2</sup>, Nobuhiko Sunahara<sup>2</sup>, Satoru Nakashima<sup>3</sup>, Takemasa Matsuda<sup>1</sup>

<sup>1</sup>Center for Rheumatic Disease, Japanese Red Cross Society Kagoshima Hospital, Kagoshima, Japan, <sup>2</sup>Center for Rheumatic Disease, Japanese Red Cross Society Kagoshima Hospital, Kagoshima, Japan, <sup>3</sup>Kagoshima Consumers Cooperative Hospital, Kagoshima, Japan

Conflict of interest: None

A 62 year old woman developed SLE and was started medication in 1991. In 2001, she suffered from lupus nephritis and NPSLE, and was treated with a steroid massive dose and cyclosporine. In April 2012, she stopped treatment with a self-judgement. She started treatment again in January 2013 because the lupus pleuritis and NPSLE recurred. She was hospitalized and received medical treatment for bacterial pneumonia at June 2014. She took PSL 22.5mg/day and tacrolimus 3mg/day. On August 19, because sensory disturbance, disturbance of consciousness occurred to her suddenly, she was admitted to our hospital. Brain abscess and muscular fasciae lower abscess were detected, and drainage was performed. Trimethoprim-sulfamethoxazole combination and minocycline was started on the #rd hospital day and she recovered. Culture of the drain pus revealed Nocardia asteroides infection. In this case, pneumonia was regarded as pulmonary nocardiosis, and was disseminated to other organs. Nocardiosis is a rare disease and we added consideration from literature and report it.

### P1-248

#### Listeria meningitis in an entero-Beçet's disease patient treated with adalimumab

Daisuke Kashiwakuma, Hirotohi Kawashima, Kentaro Takahashi, Itsuo Iwamoto, Shoji Yoshida, Shin-ichiro Kagami  
Research Center for Allergy and Clinical Immunology, Asahi General Hospital, Chiba, Japan

Conflict of interest: None

A 64-year-old male patient with entero-Beçet's disease was treated

with prednisolone and adalimumab. In late August 2014, he developed fever, watery diarrhea and headache and was admitted to our hospital. His diarrhea was improved in a few days, but headache continued and gradually worsened. Cerebrospinal fluid (CSF) test showed an increased number of neutrophils. Blood and CSF cultures grew *Listeria monocytogenes*. He was diagnosed with listeria meningitis. Adalimumab was discontinued and he was treated with ampicillin and gentamycin for six weeks. Although he recovered from listeria meningitis, severe bleeding from ileocecal ulcer was relapsed. Treatment with adalimumab and 40mg of prednisolone was started, but the bleeding was not improved. Ileocecal resection was performed. *L. monocytogenes* is an intracellular parasite and is known to cause sepsis and meningitis in immunocompromised hosts, including those on anti-TNF agents. It can be acquired through food. In this case, the patient received anti-TNF therapy and had ileocecal ulcer associated with entero-Behçet disease. The mucosal damage from entero-Behçet disease may facilitate the invasion of listeria. We report a case of listeria meningitis in an entero-Behçet disease patient treated with adalimumab.

### P1-249

#### A case of TAFRO syndrome

Takashi Maruyama, Akinori Kunibu, Takuma Wada, Yuki Shimada, Yasufumi Shindo, Yoshihiro Yoshida, Kazuhiro Yokota, Yasuto Araki, Hiroshi Kajiyama, Haruhiko Akiba, Kojiro Sato, Yuji Akiyama, Toshihide Mimura  
Saitama Medical University Hospital, Saitama, Japan

Conflict of interest: None

A 69 years old woman was admitted to our hospital because of pleural effusions, renal failure, thrombocytopenia, back pain, edema and dyspnea. Five months before admission, she was diagnosed as RS3PE syndrome at the previous hospital, because of fever, arthralgia and pitting edema in the limbs. Those symptoms were improved temporarily by administration of prednisolone (PSL) 20mg, but aggravated during tapering PSL. Furthermore, pleural effusions, renal failure, thrombocytopenia, back pain, edema, dyspnea and blindness appeared. She was transferred to our hospital. She had back pain and mild pain on the lower abdomen. Erythema were seen on her neck and chest. No lymphadenopathy was detected. The blood tests showed CRP 2.09, Cr 1.51, LDH 1089, ALP 315, IL6 62.5, leukocytes 7980, hemoglobin 13.6, and platelet was 52,000. The urine was normal. Abdominal CT revealed, bilateral enlarged kidneys, splenomegaly, pleural effusion and ascites. The diagnosis of TAFRO syndrome was made. PSL was increased to 50mg, but thrombocytopenia remained. She died of uncontrolled pneumonia. Because TAFRO syndrome is a new and rare disease, it is necessary to collect cases with this syndrome.

### P1-250

#### A Familial Mediterranean Fever with a Homozygous S503C: First Case Report

Junwa Kunitatsu<sup>1</sup>, Junko Maeda<sup>1</sup>, Dai Kishida<sup>2</sup>

<sup>1</sup>Department of General Internal Medicine, National Center for Global Health and Medicine Hospital, Tokyo, Japan, <sup>2</sup>Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Matsumoto, Japan

Conflict of interest: None

[Background] S503 is known as a mutation in FMF. However, we know little knowledge of the clinical picture of FMF patients with S503C mutation, and it is unclear how a S503 mutation functions for disease processing of FMF. [Case] A 50-year-old Japanese man presented with recurrent episodes of fever, ankle pain, cough, headache, and nonspecific chest pain. He experienced 4-week-cycled periodic fevers one year before the first visit, and he was completely healthy in attack-free intervals. Those symptoms were resolved spontaneously within 7-10 days. He had no family history of a periodic fever. The analysis of MEFV genes revealed a homozygous S503C. 0.5mg/day colchicine was administered, but during the next few days, a rash appeared and stopped colchicines. We decided to re-start colchicine with 0.25mg. He was tolerant to it, and the attacks were remitted. The diagnosis of FMF was made. [Discussion]

A S503C mutation have been overlooked and underestimated because of its rarity. We should pay more attention to mild mutations, which are potentially associated with a pathological process of atypical FMF. [Conclusion] Our case illustrated that S503C may play a role as an etiological factor and may distort the typical clinical pictures as a functional mutation.

### P1-251

#### 3 cases of Familial Mediterranean fever with various types of serositis

Kae Hamamoto<sup>1</sup>, Hitoshi Goto<sup>1</sup>, Shinsuke Yamada<sup>1</sup>, Maki Yoda<sup>1</sup>, Koichiro Yoda<sup>1</sup>, Masaaki Inaba<sup>1</sup>, Kiyoshi Migita<sup>2</sup>

<sup>1</sup>Rheumatology, Osaka City University Hospital, <sup>2</sup>Clinical Research Center, NHO Nagasaki Medical Center

Conflict of interest: None

[Background] Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by recurrent and short duration of fever, and serositis. We experienced 3 cases of FMF, which presented atypical periodic fever and various types of serositis. [Cases] The first case was 26years old female suffered from periodic fever that last for several months since she was 21years old. She had stomachache, polyarthritits, enthesitis. The second case was 42 years old female, she had persistent fever in winter since she was 34. She suffered headache, enthesitis, a right hypochondrium ache. Liver biopsy was performed and we found serositis on the capsule of liver. The third case was 40 years old female, with SLE. She had fever which persist for 3 days in once a month, and neck pain. MRI showed intensive synovitis in Atlanto-Axial Joint and synovial fluid extended to anterior side of vertebrae. Genetic analysis was performed in all cases and they all diagnosed as FMF variant. Colchicine (0.5-2.0 mg/day) was effective in all the cases. [Discussion] As they had various serositis and their symptom were atypical, several years were needed for the diagnosis of FMF. [Conclusion] We need to consider about FMF when we see the patient who shows various symptoms accompanied by periodic fever.

### P1-252

#### A case of Familial Mediterranean Fever (FMF) with recurrent leucopenia

Shun Minatoguchi<sup>1</sup>, Toshikazu Ozeki<sup>1</sup>, Mitsuru Watanabe<sup>2</sup>, Yukari Murai<sup>1</sup>, Rui Kawato<sup>2</sup>, Akihiro Ryuge<sup>1</sup>, Koji Takasugi<sup>2</sup>, Takuya Hamada<sup>3</sup>, Yukako Oyama<sup>1</sup>, Atsushi Nomura<sup>2</sup>, Tatsuhiro Tomino<sup>2</sup>, Hideaki Shimizu<sup>1</sup>, Yoshiro Fujita<sup>2</sup>, Kiyoshi Migita<sup>4</sup>

<sup>1</sup>Department of Nephrology, Chubu Rosai Hospital, Nagoya, Aichi, Japan, <sup>2</sup>Department of Rheumatology, Chubu Rosai Hospital, Nagoya, Aichi, Japan, <sup>3</sup>Department of Internal Medicine, Chubu Rosai Hospital, Nagoya, Aichi, Japan, <sup>4</sup>Department of Clinical Research Center, NHO Nagasaki Medical Center, Nagasaki, Japan

Conflict of interest: None

FMF is auto-inflammatory disorders that cause febrile attacks and serositis. We report a case of FMF with recurrent leucopenia. <CASE> Forty three year old man was admitted because of persistent fever. He has a history of acute pancreatitis 5 years ago. He had low-grade fever in mid-April 20XX and was diagnosed as a common cold. But low-grade fever was persistent and he had high fever from beginning of May, then he was admitted. On admission, CRP and neutrophils were 0.81mg/dL and 900/ $\mu$ L, respectively. A week after admission, fever was decreased spontaneously, but leucopenia deteriorated to 500/ $\mu$ L. Leucopenia resolved without any treatment. A month after the first admission, the same episode of fever and leucopenia occurred. Due to the periodic episodes, we suspected FMF. So we checked the MEFV gene, and the test revealed a compound heterozygous mutation (P369S/R408Q) which suggested FMF variant. We administered colchicine and the attack of fever and leucopenia was disappeared. <Clinical implication> In our case, colchicine cleared fever attacks and leucopenia. It suggests the correlation between leukopenia and FMF. FMF should be considered in patients with unidentified fever and intermittent leucopenia



### P1-253

#### Genetic polymorphisms of inflammation factors in Japanese patients with Palindromic rheumatism

Hayate Tanaka<sup>1</sup>, Ayaka Ise<sup>1</sup>, Aya Kawase<sup>1</sup>, Yumiko Masago<sup>1</sup>, Chiharu Sawada<sup>1</sup>, Koji Inoue<sup>2</sup>, Shunichi Shiozawa<sup>3</sup>, Koichiro Komai<sup>1</sup>

<sup>1</sup>Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, <sup>2</sup>Shichikawa Arthritis Center Osaka Rehabilitation Hospital, Hannan, Osaka, Japan, <sup>3</sup>Kyushu University Beppu Hospital, Beppu, Oita, Japan

Conflict of interest: None

[Objectives] Palindromic rheumatism (PR) is an inflammatory syndrome characterized by periodic acute arthritis. Although genetic factors are thought to be associated with PR, the details are still unclear in Japanese patients. Here, we describe about genetic polymorphisms in candidate inflammation factors, including *PYCARD* (ASC), *PSTPIP1* and *TNFRSF1A*. [Methods] The subjects were three Japanese female patients with PR. They developed PR at 17, 57 and 22 years old respectively. One of them was sporadic and two of them are mother and daughter. We isolated the coding region of *PYCARD* (ASC), *PSTPIP1* and *TNFRSF1A* gene from peripheral blood, and performed sequence analysis. [Results] Normal type *PYCARD* (ASC) gene was not expressed in all of patients, but we found that the portion of sequence deficient *PYCARD* (ASC) variant was dominantly expressed in all of patients. There were no sequence differences in *PSTPIP1* and *TNFRSF1A* between the patients with PR and healthy controls. [Conclusion] Our results suggest that the variant *PYCARD* (ASC) affects inflammasome function and associate with pathogenesis of PR.

### P1-254

#### Two adult cases of Cryopyrin-associated periodic syndrome (CAPS) successfully treated with Canakinumab

Kumiko Shimoyama<sup>1</sup>, Hiroyuki Ohashi<sup>2</sup>, Ryuta Nishikomori<sup>3</sup>, Daisuke Suzuki<sup>1</sup>, Tamaki Sagisaka<sup>2</sup>, Noriyoshi Ogawa<sup>1</sup>

<sup>1</sup>Third Department of Internal Medicine, Hamamatsu University School of Medicine, <sup>2</sup>Omazeki Municipal Hospital, <sup>3</sup>Department of Pediatrics, Kyoto University Graduate School of Medicine

Conflict of interest: None

We report two cases of Cryopyrin-associated periodic syndrome (CAPS) treated with Canakinumab. Case 1: A 38-year-old male found to have anemia, leukocytosis and elevation of CRP at a medical check-up. Urticaria-like skin lesions were developed since several months after birth and hearing disturbance and fever were developed in his 30's. His mother, grandparents, uncles, and aunts also had similar symptoms. He had frontal bossing, arthritis, injection of eyes, elevation of serum amyloid A (SAA) protein, and meningitis. Low dose corticosteroid, Tocilizumab were effective for inflammation, however, they were not effective for skin lesions, headache or arthritis. Case 2: A 59-year-old female found to have anemia, leukocytosis, and elevation of CRP at a medical check-up. Urticaria-like skin lesions, arthritis and hearing disturbance were developed in her 10's. Her father, brothers and sisters also had similar symptoms. She had frontal bossing, elevation of SAA. They were diagnosed as having CAPS by CIAS-1 gene analysis. Canakinumab was started and remission was achieved in both cases. Some cases with CAPS are diagnosed in their adulthood. It should be important to make a correct diagnosis as early as possible, and to use Canakinumab to induce remission.

### P1-255

#### Two cases of X-linked agammaglobulinemia with symptoms suggested as autoinflammation

Atsuyoshi Morishima<sup>1</sup>, Toru Hirano<sup>1</sup>, Masashi Narazaki<sup>1</sup>, Yoshihito Shima<sup>1</sup>, Atsushi Ogata<sup>1</sup>, Toshio Tanaka<sup>2</sup>, Atsushi Kumanogoh<sup>1,3</sup>, Jun Nakata<sup>1,5</sup>, Naoki Hosen<sup>4</sup>

<sup>1</sup>Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Graduate School of Medicine, Suita, Osaka, Japan, <sup>2</sup>Department of Clinical Application of Biologics, Osaka University Graduate School of Medicine, Suita, Osaka, Japan, <sup>3</sup>Japan Science and Technology, Core Research for Evolutional Science and Technology

(CREST), Osaka University, Suita, Osaka, Japan, <sup>4</sup>Department of Cancer Stem Cell Biology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan, <sup>5</sup>Department of Cancer Immunotherapy, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

Conflict of interest: None

X-linked agammaglobulinemia (XLA) is a disease which impairs the differentiation of B cells because of the Btk gene abnormalities on the X chromosome, leads to the impairment of immunoglobulin (Ig) production. We experienced two cases who presented refractory and aseptic systemic inflammation in spite of immunodeficiency. Case 1 was a male patient, and had received Ig infusions regularly. When he was 40, he began to suffer aseptic systemic arthritis and fever without the rise of specific antibody. He was treated by steroids, however the inflammation did not decrease, and persisted. Case 2 was a male patient, and had received Ig infusions regularly. When he was 28, he began to suffer aseptic skin ulcer of a lower leg and fever without the rise of specific antibody. He was treated by steroids, cyclosporine and infliximab, however the inflammation was not controlled. These two cases accord with that primary immunodeficiency contains autoinflammatory syndrome as is defined recently.

### P1-256

#### The relation between the onset of deep venous thrombosis, dilation of soleal vein and the existence of "smoke-like echo" in ultrasonography during perioperative period of total knee arthroplasty

Masamichi Tahara, Ken-ichiro Goto

Dept. of Orthop. Surg., National Hospital Organization Chiba East Hospital, Chiba, Japan

Conflict of interest: None

[Objectives] To investigate the relation between DVT formation, dilation of soleal vein and the existence of "smoke-like echo" which would appear retention of blood flow in ultrasonography during perioperative period of TKA. [Methods] We examined 94 patients with osteoarthritis and rheumatoid arthritis who undergo TKA. Venous ultrasonography of lower extremity were performed before and two weeks after surgery. The diameter of soleal vein was evaluated in the sitting position. We also checked the existence of "smoke-like echo" in soleal vein. Perioperative prophylaxis consisted of a pneumatic compression device and administration of anti-coagulant. [Results] Preoperative mean diameter of soleal vein significantly was larger in cases having DVT postoperatively (DVT+: average 7.8mm, DVT-: average 5.88mm). In addition, the perioperative mean diameter of soleal vein was significantly dilated in cases appearing "smoke-like echo" (echo+: average 8.48mm, echo-: average 5.61mm). [Conclusion] The dilation of soleal vein in ultrasonography was correlated with existence of "smoke-like echo" and perioperative DVT formation in patients undergoing TKA.

### P1-257

#### Initial management of acute inflammatory arthritis at a municipal hospital in Japan

Sanshiro Inoue

Department of Orthopedic Surgery, Fukuoka Higashi Medical Center, Koga, Japan

Conflict of interest: None

[Objectives]to research the acute inflammatory arthritis and discuss the initial management at our hospital. [Methods] Thirty-one cases (18 men and 13 women) with acute inflammatory arthritis (CRP >1.0mg/dl) were evaluated. Their mean age was 65.2±25.4 years old (4-95). Seven patients had polyarthritis. There are 6 patients with a final diagnosis of septic arthritis, 7 with gout, 7 with pseudogout, 2 with collagen disease and 9 with other etiologies. Arthrocentesis were performed in 28 cases and 10 underwent surgery. The patients were divided into two groups; infection group or non-infection group. The factors that might predict infection were investigated. The factors included age, sex, past history, the time when patients visited our hospital, the number of affected joints, laboratory findings. The Fisher exact test and Man-Whitney test were used. Significance was assumed at P-value < 0.05. [Results] There was

no factor that showed significance in this study. [Conclusion] The points of initial treatment may be as follows; 1Septic arthritis should be always kept in mind. 2It is critical to analyze joint fluid and culture it. 3Presence of crystals is not an evidence of absence of infection. 4Prolonged antibiotic treatment for non-inflammatory disease should not be continued.

### P1-258

#### Successful improvement in three cases of proximal femoral fracture treated with denosumab

Masanori Nakayama, Hiroya Kanagawa, Osahiko Tsuji  
Department of Orthopaedic Surgery, Saitama Medical Center, Japan  
Community Health Care Organization

Conflict of interest: None

[Objective] We report three cases who have successful improvement in three cases of proximal femoral fracture treated with denosumab. [Methods and Results] Case 1. 83yo F. She was as diagnosed as femoral neck fracture and denosumab was administered to her 2 weeks after hospitalization. She became to relief from pain of motion of hip after a week and she began gait exercise with full load after more 2 weeks. She was able to walk with walker by herself, and she discharged from hospital 5 weeks after administration. Case 2. 86yo F. She was diagnosed as proximal femoral fracture and denosumab was administered to her after a week. Pain of motion diminished a week after administration. She could gradually pull herself up to walk and transfer herself from bed to wheel chair by herself, and she moved to rehabilitation hospital 7weeks after administration. Case 3. 95yo M. Denosumab was administered to him three days after diagnosis. Pain of motion diminished three weeks after administration. He could gradually transfer himself from bed to wheel chair by himself, and he moved to nursing home after 4 weeks. [Conclusion] In these cases, hip pain diminish comparatively soon and they were going to undergo gait exercise. The results support the efficacy of denosumab to proximal femoral fracture.

### P1-259

#### A case of a rheumatoid arthritis patient whose chief complaint was a mass of the right shoulder

Erabu Miyamoto<sup>1</sup>, Hideto Nishi<sup>1</sup>, Ryosuke Sakata<sup>2</sup>, Munehito Yoshida<sup>1</sup>  
<sup>1</sup>Wakayama Medical University Hospital, Wakayama, Japan, <sup>2</sup>Wakayama Rosai Hospital, Wakayama, Japan

Conflict of interest: None

In June 2012, a 62-year-old male noticed the mass in his right shoulder. Because it grew big, he consulted the specialist in tumor of our department in September 2012. At the first medical examination, the marginal clear elastic soft mass of the 11×10cm size was palpated in the anterior surface of his right shoulder. We performed needle biopsy and incisional biopsy, but we did not lead to a diagnosis. The mass grew big, we planned the complete removal of the mass in July, 2014. By a medical examination at admission, swelling was found in his wrists and MCP joints, swan neck deformity of both fingers and hallucal Z-shaped transformations were found, too. Sthenia of the inflammatory reaction was found in the blood test, in CRP 0.73mg/dl, ESR 67mm/1h. The anti-CCP antibody was high level-positive with 507U/ml. He was diagnosed as being rheumatoid arthritis. The histopathology of the mass which we resected was the cysts-formed lesion which continues to synovial membrane. Extensive lymphocytes and plasma cells invasion and vascular hyperplasy were found and did not contradict it as histology of rheumatoid arthritis. We thought that we should consider the rheumatoid arthritis as differential diagnosis of the soft part mass.

### P1-260

#### The immune-regulatory effect of eldelcalcitol in patients with rheumatoid arthritis

Haruka Tsuchiya, Yukiko Iwasaki, Mihoko Shibuya, Yumi Yamaguchi, Shuji Sumitomo, Keishi Fujio, Kazuhiko Yamamoto  
Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Conflict of interest: None

[Objectives] The aim of the present study was to evaluate the immune-regulatory effect of eldelcalcitol in patients with rheumatoid arthritis (RA). [Methods] Thirteen vitamin D naïve RA patients were administered with eldelcalcitol. Clinical parameters (IgG, IgA, IgM, Rheumatoid factor and CRP) were measured before and after treatment. Serum concentrations of cytokines (GM-CSF, IFN $\gamma$ , IL-10, IL-17A, IL-1 $\beta$ , IL-21, IL-6 and TNF $\alpha$ ) were analyzed by Bio-Plex™ Cytokine Assay (Bio-Rad). Other drugs that affect bone metabolism or immune system were not changed during this study. [Results] The serum levels of immunoglobulins showed a tendency to decrease at 3 months especially for patients with basal vitamin D deficiency (IgG; p=0.03, IgA; p=0.004). Furthermore, among the patients who exhibited a significant decrease of 1,25-(OH)2D levels after treatment, a moderate positive correlation was found between the amount of change of 1,25-(OH)2D and some cytokines at 6 months (IL-17A; r=0.54, IL-1 $\beta$ ; r=0.61, IL-6; r=0.5). [Conclusion] In this study, the immune-regulatory effect of eldelcalcitol was suggested and it could be beneficial not only for management of osteoporosis but also for autoimmune disease.

### P1-261

#### Contribution of genetic factors other than transporter genes in the development of gout

Naomi Ichikawa, Atsuo Taniguchi, Chieko Sekita, Hirotaka Kaneko, Hikota Osawa, Yohei Seto, Hisashi Yamanaka  
Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: None

[Background] Genome-wide association studies (GWAS) have recently identified polymorphisms on several loci that are associated with serum uric acid levels (SUA). Many of these genetic factors are the polymorphisms of genes that code transporters expressed in renal tubules. However, recently, genetic factors other than transporter genes have been reported to be associated with SUA. [Objective] The aim of this study was to investigate the association of genetic factors other than transporter genes with gout in Japanese. [Method] The subjects were 326 Japanese patients with gout and 597 controls. We selected genes other than transporter genes that have previously been reported to be associated with SUA or gout; *PZDK1*, *RREB1*, *MTHFR*, *INHBC*, *MAF*, and rs1333049. [Results] There was no difference in allele frequency of polymorphisms in *RREB1*, *MTHFR*, *MAF*, or rs1333049 between gout patients and controls. Although no differences of allele frequencies in *PZDK1* or *INHBC*, genotypic analyses of these genes showed significant associations with the development of gout. [Conclusion] It was suggested that *PZDK1* and *INHBC* were contribute to the development of gout in Japanese.

### P1-262

#### Sarcopenia in patients of rheumatoid arthritis

Kazushi Haraguchi  
Department of Orthopaedic Surgery Japan Seafarers Relief Association Moji Ekisaikai Hospital, Kitakyushu, Japan

Conflict of interest: None

[Objectives] In late years interest in sarcopenia is increasing. we investigate sarcopenia in our RA patients. [Methods] 58 RA out-patients (15 male, 43 female) who received a total body scan by DXA were investigated. 275 cases (30 male, 245 female) except RA a target for comparison. SMI (Skeletal muscle mass index) kg/m<sup>2</sup> was used for an evaluation of the muscle mass. Following the Asian Sarcopenia Working group diagnostic criteria (except walking speed), the ratio of patient with sarcopenia was compared RA with a target for comparison. SMI% was assumed the ratio with the measured SMI of and the SMI of diagnostic criteria (7.0 kg/m<sup>2</sup> of male, female 5.4 kg/m<sup>2</sup>). For RA patient, correlations of SMI % and age, stage, class, disease duration, DAS and HAQ were investigated. [Results] 38 cases (65.5%) corresponded to sarcopenia in RA and 61 cases (22.2%) in other. The correlation coefficients with SMI % were age (-0.25), stage (-0.32), class (-0.46), disease duration (-0.29), DAS (-0.12), HAQ (-0.29). [Conclusion] The muscle atrophy of the RA patient was considered to be secondary with the joint functional disorder, and this re-

sult was not a thing in conflict with it. The ratio of sarcopenia is high in RA patients, and it is necessary to future examination.

### P1-263

#### Sub-classification of 140 patients with psoriatic arthritis

Kiyofumi Hagiwara<sup>1</sup>, Yasuhiro Suyama<sup>1</sup>, Kunihiko Fukuda<sup>2</sup>

<sup>1</sup>Department of Rheumatology, JR Tokyo General Hospital, <sup>2</sup>Department of Radiology, The Jikei University School of Medicine

Conflict of interest: None

[Objectives] To sub-classify patients with psoriatic arthritis (PsA). [Methods] 140 patients who strictly fulfilled classification criteria for psoriatic arthritis (CASPAR) were investigated. They were sub-classified on the basis of diagnostic process and serological markers. [Results] Pattern A: 96 patients, who had not have a definite diagnosis, were diagnosed as having PsA for the first time. Labo data of most of them showed seronegative and low-inflammatory response pattern. Pattern B: 26 patients, who had initially had a diagnosis of rheumatoid arthritis (RA), were re-diagnosed as having PsA. Labo data of all of them showed seropositive pattern. Pattern C: 18 patients, who had initially had a diagnosis of polymyalgia rheumatica (PMR) or remitting seronegative symmetrical synovitis with pitting edema (RS3PE), were re-diagnosed as having PsA. Labo data of all of them showed seronegative and high-inflammatory response pattern. [Conclusion] To date, PsA mimicking PMR/RS3PE or the coexistence with PsA and PMR/RS3PE has not been described. When PMR/RS3PE is suspected, it is necessary to perform thorough physical/radiological examinations and to check the coexistence with PsA.

### P1-264

#### Development of database cooperation system for rheumatoid arthritis

Ryuichi Nakahara<sup>1</sup>, Keiichiro Nishida<sup>2</sup>, Kenzo Hashizume<sup>1</sup>, Ryoza Harada<sup>1</sup>, Takahiro Machida<sup>1</sup>, Masahiro Horita<sup>1</sup>, Toshifumi Ozaki<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, <sup>2</sup>Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Conflict of interest: Yes

[Objectives] Database structure is different for each hospital, so database construction is required for each multicenter study. We have developed computer tablet based clinical data input and statistical analysis system which can work on the electronic medical record system. In order to solve this problem, we developed database cooperation system by adding a database link function to this system. [Methods] We have created three types of database (database A, B, C) which structure is different each other. Randomly generated number were used as a test data. To verify the data sharing system, we anonymously aggregated sub dataset of database B and C to database A. [Results] Correspondence table, conversion table, and arithmetic system enabled the connection of different types of databases. In database A, we can perform various kinds of statistics and graph plotting. [Conclusion] We developed database cooperation system, which can connect anonymously different types of databases.

### P1-265

#### The role of the clinical research coordinator in post marketing surveillance

Yoshimi Amano<sup>1</sup>, Kenta Misaki<sup>2</sup>, Rintaro Saito<sup>2</sup>, Yuri Nakamura<sup>2</sup>, Yoshie Gon<sup>2</sup>, Takumi Nagamoto<sup>2</sup>, Hisayo Horiuchi<sup>2</sup>, Hirotaka Yamada<sup>2</sup>, Toshihiko Yokota<sup>2</sup>

<sup>1</sup>Department of Clinical Research Division, Kurashiki Central Hospital, Okayama, Japan, <sup>2</sup>Department of Endocrinology and Rheumatology, Kurashiki Central Hospital, Okayama, Japan

Conflict of interest: None

[Objectives] Post marketing surveillance (PMS) can necessitate navigation through complex hospital procedures and long-periods of time. Physicians undertaking PMS outside of regular practice is frequent, thus

reducing this burden with the clinical research coordinator (CRC) is important. To clarify the future role of the CRC in the PMS process, we reviewed data of time spent on CRC by physicians. [Methods] From Sep. 2010 to Oct. 2014, the Department of Rheumatology undertook 8 PMSs with 20 patients. Time consisted of registration (30 min/patient), physician questioning (1 hr/5 pages), patient survey (30 min/survey), adverse event investigation (1 hr/case), and physician reinvestigation (1 hr/case). [Results] Total necessitated annual hrs of PMS were 2010 (PMS 2, patients 1), 2011 (PMS 5, patients 9), 2012 (PMS 7, patients 13), 2013 (PMS 6, patients 7), and 2014 (PMS 4, patients 7). Total time required in all cases of PMS was 291.5 hrs (2010 19 hrs, 2011 79.5 hrs, 2012 68.5 hrs, 2013 59.5 hrs, 2014 65 hrs). [Discussion] The average time required by PMS annually was 70 hrs/year, thus we considered CRC could reduce the time spent on PMS by physicians. The role PMS and the CRC play in pivotal role for the evaluation the long-term and adverse effects of drugs will be essential.

### P1-266

#### The effect of the introduction of scheduled education about the prevention of infection to rheumatoid arthritis patients who are treated with biologic agents on patient knowledge and behavior

Kaori Hisazawa, Mayu Hisano, Mihoko Watari, Kazuyo Waseda  
Japanese Red Cross Kagoshima Hospital, Kagoshima, Japan

Conflict of interest: None

[Objectives] The purpose of this study is to clarify whether the change of patient education methods increases patient knowledge about the side effects of biologic agents and the practice rate of the infection prevention action. [Methods] We changed patient education methods from unscheduled education to scheduled education (once a year). Moreover, after every education, we tested patient knowledge by using a questionnaire. By using new methods, we educated 107 patients during the period from August 1, 2013 through July 31, 2014. [Results] After the change of education methods, patient knowledge about the side effects of biologic agents and the practice rate of the infection prevention action were increased. Moreover, patient knowledge about the necessity of discontinuation of methotrexate in bad physical condition was also increased. The most common cause of a postponement of biologic agent administration was acute upper respiratory tract infection. However, the rate of it was decreased after the change of education methods. [Conclusion] The change of patient education methods increased the practice rate of the infection prevention action and patient knowledge about the side effects of biologic agents, the symptoms of infection and methods for dealing with infection.

### P1-267

#### Challenge for infection risk reduction to rheumatoid arthritis patients in the nursing education

Ikuyo Noguchi, Kosaku Oda  
Department of Orthopedic Surgery, Takatuki Red Cross Hospital, Osaka, Japan

Conflict of interest: None

[Objectives] Preventing the occurrence of serious adverse event and understanding the infection risk of rheumatoid patients by nursing education (NE). [Methods] We investigated patients received questionnaire and their own medical records about the presence of infectious diseases from 2012 to 2013 in 70 RA patients by NE. [Results] The results showed patients complete understanding the side effects using strong DMARDS or biologics. The level of comprehension and satisfaction was very high and almost needed explanations. Most of infection were common cold. The treatment period were 5 to 7 days in most. Whether became susceptible to infection or not, 53% were not feel particularly, and 24% became susceptible. About of skipped DMARDS and biologics in infection, 53% patients were able to continue treatment without skipping in early medical examination. When patients affected the infection, they usually visit attending physician or nurse. After training NE, the incidence of common cold was reduced but gastroenteritis and flu herpes increased slightly. [Conclusion] Dealing with adverse events made possible to understand by most patients. However patients cannot judge AE by

themselves. Therefore continued education by nurses is very important.

## P1-268

### Construction of RA network in Gunma Prefecture; GRN

Koichi Okamura<sup>1,2</sup>, Yukio Yonemoto<sup>1,2</sup>, Tetsuya Kaneko<sup>1,2,3</sup>, Yasuyuki Tamura<sup>2,3</sup>, Masatoshi Matsushita<sup>2,4</sup>, Kimihiko Takeuchi<sup>2,4</sup>, Keio Ayabe<sup>2,5</sup>, Hiroshi Inoue<sup>2,3,6</sup>, Takenobu Iso<sup>2,6</sup>, Kenji Takagishi<sup>1,2</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine, Gunma, Japan, <sup>2</sup>Gunma RA Network, <sup>3</sup>Inoue Hospital, <sup>4</sup>Ise-saki Fukushima Hospital, <sup>5</sup>Keiyu Orthopedic Hospital, <sup>6</sup>Gunma RA Clinic

Conflict of interest: None

[Objectives and Methods] While the medical treatment for rheumatoid arthritis (RA) has been changed, evidences for performing better medical treatment is needed, and the multicenter clinical studies need to be accumulated for that purpose. In addition, we have to give information of RA to the patients and general public. Therefore, we established the multi-institution database with five RA clinics, one belongs to the University Hospital, three orthopedics hospital, and one rheumatism special clinic (non-floor). The name of this database was named as GRN. After the approval of the Ethics Committee, we established GRN and gathered information among these institutes. As a data collection, after anonymity of patient information, each institution sent view tables (medical examination views, laboratory data, HAQ, etc.) to a GRN secretariat via cloud service. [Result] The collected data were inputted into forms which the GRN secretariat created using database management software. We analyzed the clinical data and gave the presentations in the previous JCR and EULAR annual meetings. [Conclusion] This database is used to collect the clinical data of multiple institutions, therefore the collected clinical data might be useful for the rheumatoid physicians, RA patients and general public.

## P1-269

### Our hospital and clinic cooperation on management of rheumatoid arthritis patients and the satisfaction surveys 1 year after

Yoko Imoto<sup>1</sup>, Norie Suganuma<sup>1</sup>, Toshiyuki Aramaki<sup>2</sup>, Kaoru Terada<sup>2</sup>, Yukitaka Ueki<sup>2</sup>

<sup>1</sup>Nursing Section, Sasebocho hospital Center for Rheumatic Disease, <sup>2</sup>Sasebocho hospital Center for Rheumatic Disease

Conflict of interest: None

[Background and Objectives] Our hospital is in the northern area of Nagasaki Prefecture and we cared rheumatic disease patients. We started to build the hospital and clinic cooperating system named 'Ra-Ra Circle' in 2011. In this system, a family doctor treat a RA patient and the rheumatologist and medical staffs in our hospital meet and advise patients every 3 to 6 months using a unique files. We have cooperated with sixty-five clinics and one hundred twenty-seven patients have been supported. To improve our system, we made patients' satisfaction surveys. [Method] We performed a questionnaire for 79 patients who have been followed at least 1 year. The satisfaction was assessed using VAS scale, scoring 0 to 10 points. We investigated about seven items such as the specialty, the waiting time, and the convenience to visit. [Results] The average of the degree of patients' satisfaction is 8.2 points to our hospital. A item 'the specialty' got high score 9.2 points, and 'the nurses' advises of every visit' item got 8.7 points. The average is 7.4 points to the family doctor, a high score item was 'convenient to visit'. [Conclusion] In order to manage the RA patients more better, We will share this survey results and consider how we care the RA patients with the family doctors.

## P2-001

### Predictors of patient's global assessment (PGA) in rheumatoid arthritis patients: cross-sectional and 1-year longitudinal analysis in a large observational cohort in Japan

Hideyuki Watanabe<sup>1,2</sup>, Masao Katayama<sup>3</sup>, Tomoya Miyamura<sup>1</sup>, Akie Hirata<sup>1,4</sup>, Yasuo Suenaga<sup>5</sup>, Eiichi Suematsu<sup>1</sup>, Shigeto Tohma<sup>6</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine,

Saiseikai Iizuka Kaho Hospital, <sup>3</sup>Division of Rheumatology, Department of Internal Medicine, National Hospital Organization Nagoya Medical Center, <sup>4</sup>Department of Geriatric Medicine, Graduate School of Medical Sciences, Kyushu University, <sup>5</sup>Department of Rheumatology, National Hospital Organization, Beppu Medical Center, <sup>6</sup>Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami-hara National Hospital, Sagami-hara, Japan

Conflict of interest: None

[Objectives] To examine the predictor of patient's global assessment (PGA) in patients of rheumatoid arthritis (RA). [Methods] We analyzed 3,107 RA patients who completed the Hospital Anxiety and Depression Scale (HADS) and EuroQoL (EQ-5D) questionnaires, an index of the QOL, using database of a large observational cohort study (*NinJa* 2012-13). Determinants of PGA were ascertained by multivariate logistic regression, adjusting for swollen joint counts (SJC), tender joint counts (TJC), CRP and ESR as disease activity index. Predictors of 1-year change in PGA were examined by multivariate-adjusted linear regression. [Results] In the group which satisfied 3 out of 4 items of the Boolean remission standard, 73% of patients did not meet PGA. EQ-5D was related to PGA exacerbation (OR 0.38, 95%CI 0.30-0.46). In patients who did not meet the PGA criterion despite of a good clinical disease state (n=1,515), HADS was also significantly related to PGA. In addition, worsening of PGA significantly related with worsening of EQ-5D, SJC, TJC and ESR. [Conclusion] The PGA was strongly influenced by QOL as equal as disease activity. In patients with RA who do not fulfill the Boolean remission criteria for PGA, assessment of effect of anxiety and depression should be considered.

## P2-002

### Association between physical function and patient's global assessment (PGA) among RA patients in National Database of Rheumatic Diseases in Japan -Effect modification of PGA on the association of disease activity and physical function-

Akie Hirata<sup>1,2</sup>, Masao Katayama<sup>3</sup>, Tomoya Miyamura<sup>1</sup>, Hideyuki Watanabe<sup>1,4</sup>, Yasuo Suenaga<sup>5</sup>, Eiichi Suematsu<sup>1</sup>, Shigeto Tohma<sup>6</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan, <sup>2</sup>Department of Geriatric Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, <sup>3</sup>Division of Rheumatology, Department of Internal Medicine, National Hospital Organization Nagoya Medical Center, Nagoya, Japan, <sup>4</sup>Division of Rheumatology, Department of Internal Medicine, Saiseikai Iizuka Kaho Hospital, Kaho, Japan, <sup>5</sup>Department of Rheumatology, National Hospital Organization, Beppu Medical Center, Beppu, Japan, <sup>6</sup>Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami-hara National Hospital, Sagami-hara, Japan

Conflict of interest: None

[Objectives] To ascertain the association between mHAQ and PGA, and the effect modification of PGA on the association of mHAQ with known determinants of physical function, considering with patient's psychological state (HADS) and QOL (EQ-5D). [Methods] In the large observational database of *NinJa* (National database of rheumatic diseases by iR-net in Japan), 7726 RA patients were analyzed. The association between higher mHAQ and higher PGA and interaction between PGA and other factors were evaluated using multiple logistic regression. [Results] PGA was positively associated with mHAQ, independently of TJ, SJ, and ESR (Adjusted OR 5.1; 4.6-5.7). Statistically significant interaction was shown between PGA and TJ, SJ (P<0.001, P=0.04). When specified by PGA, among patients with lower PGA adjusted ORs for higher mHAQ were TJ 2.5 (2.1-2.9) and SJ 1.2 (1.0-1.4). While among patients with higher PGA, adjusted OR of TJ was 1.6 (1.3-1.9) and SJ had no significant association with mHAQ. Patients with higher PGA had higher medians of HADS and lower median of EQ-5D, compared to patients with lower PGA. [Conclusion] PGA was associated with mHAQ, modified the relation of activity with mHAQ. Physical function of patients with high PGA should be evaluated in consideration of psychological state and QOL.

## P2-003

### Change over the years of QFT in the patients of rheumatoid arthritis part2

Takuya Nakazawa, Hidekazu Futami, Ryutarō Matsumura  
Center of Rheumatology, Allergy and Clinical Immunology, National Hospital Organization Chiba East National Hospital

Conflict of interest: None

[Objectives] Methotrexate (MTX) is an anchor drug to rheumatoid arthritis (RA), use limit was up to 16 mg per week from 2011 in Japan. They demand verifying tuberculosis check test including quantiFERON-TB Gold test (QFT test) in the accompanying document of the medicine. We haven't gotten an answer that QFT test is useful to immunosuppressed patients with long-term use biologics and MTX yet. It hasn't shown what kinds of change happen in arthritis patients treated with MTX and biologics for long years. [Methods] We carried out the QFT test to RA outpatients at our hospital from 2011. The QFT test results were compared to those of next test. [Results] QFT test positive patients were twelve at the first test in the patients out of the 104 RA patients. Seven of twelve patients were examined for QFT test next test. Three patients kept positive in QFT test. Three of the patients changed negative. Anti-TB drugs were administrated to QFT test positive persons from the first test. No patient QFT test changed positive in the first test to second test. [Conclusion] The majority of subject QFT tests turned negative from positive. It suggested some influence of medication to RA. It is estimated QFT test is good index to the activity of tuberculosis in patients with RA.

## P2-004

### In palindromic rheumatism, older age, shorter interval between attacks and positive anti-CCP antibodies may predict progression to RA

Masatoshi Hayashi<sup>1,3</sup>, Toshihisa Kanamono<sup>1</sup>, Toshihisa Kojima<sup>2</sup>, Nobunori Takahashi<sup>2</sup>, Koji Funahashi<sup>2</sup>, Naoki Ishiguro<sup>3</sup>

<sup>1</sup>Departments of Rheumatology, Nagano Red Cross Hospital, Nagano, Japan, <sup>2</sup>Departments of Orthopedics Surgery and Rheumatology, Nagoya University Graduate School of Medicine, Nagoya, Japan, <sup>3</sup>Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, Leeds, United Kingdom

Conflict of interest: None

[Objectives] Palindromic rheumatism (PR) is a clinical syndrome characterised by episodes of joint swelling that settle spontaneously. A proportion of patients with PR progress and develop rheumatoid arthritis (RA). We therefore identified potential factors associated with the development of RA in these patients. [Methods] A retrospective analysis was done on 55 patients with PR followed up in our rheumatology early arthritis clinics. Medical history, clinical examination and laboratory findings were compared between the group that progressed to ACR/EULAR 2010 RA (progression) and the group that did not (non-progression). [Results] Of the 55 patients, 28 (51%) developed RA and 27 (49%) did not over a mean (SD) period of 28.3 (40.0) and 17.2 (19.0) months of follow-up. Factors that differed between the groups were: age at PR onset (non-progression vs. progression median 48 vs. 39 years), duration of interval between attacks (30 vs. 45 days), anti-cyclic citrullinated peptide (anti-CCP) positivity (96% vs. 73%), and anti-CCP titre (164 vs. 57 U/ml). [Conclusion] Features on history and anti-CCP anti-body positivity, particularly high antibody titres, were found to be associated with evolution to RA. These data should be of value in managing therapy and follow-up of PR patients.

## P2-005

### Association of alcohol consumption with disease activity in Japanese patients with RA using IORRA cohort

Yoko Shimizu, Kumi Shidara, Eiichi Tanaka, Eisuke Inoue, Rei Yamaguchi, Akiko Kobayashi, Naoki Sugimoto, Daisuke Hoshi, Eri Sato, Yohei Seto, Ayako Nakajima, Shigeki Momohara, Atsuo Taniguchi, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: None

[Objectives] To examine the relationship between alcohol consumption and RA disease activity. [Methods] Subjects were RA patients who participated in the IORRA study for the first time between 2007 to 2012. Patients were divided into 6 groups by alcohol drinking status at baseline; non-drinking, past drinking, and drinking groups 1) ( $0 < \text{amount of drinking} \leq 14\text{g/day}$ ), group 2) ( $14\text{-}28\text{g}$ ), group 3) ( $28\text{-}50\text{g}$ ) and group 4) ( $50 <$ ). Multiple regression analyses were used to examine the relationship between alcohol consumption and baseline DAS28 or change in DAS28 from baseline to 1 year. [Results] A total of 2,369 patients were analyzed. The number of the patients (%female, mean DAS28 at baseline) were 1,436 (90.5%, 3.6), 294 (83.3%, 3.9), 263 (79.5%, 3.3), 124 (66.1%, 3.2), 111 (58.6%, 3.4), and 114 (49.1%, 3.3) in the non-drinking, past drinking, and drinking group 1), 2), 3) and 4), respectively. Multivariate regression analysis confirmed baseline DAS28 in the drinking groups 1) and 2) were significantly lower than that in the non-drinking group. There were no association between alcohol drinking and change in DAS28 from baseline to 1 year. [Conclusion] Although alcohol consumption was associated with baseline DAS28, alcohol drinking status was not associated with response to RA treatment.

## P2-006

### The analysis of background diseases and course of pregnancy in 71 cases with collagen disease at Tokyo Metropolitan Tama Medical Center

Satoshi Watanuki, Kota Shimada, Takayasu Kise, Kae Onishi, Yuji Miyoshi, Yoshiki Nagai, Eigo Kikuchi, Takahiro Nunokawa, Katsuaki Shirotō, Naoto Yokogawa, Shoji Sugii

Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center

Conflict of interest: None

[Purpose] We analyzed the background diseases and course of pregnancy (treatment and fetal complications) in 71 cases with collagen disease (CD) at our hospital for the purpose of managing future cases. [Method] Of the 5184 women who underwent delivery at our hospital between March 1, 2010 and June 30, 2014, 71 cases in whom a CD was diagnosed were retrospectively analyzed. [Results] Of the 71 cases were reviewed, (SLE 28, RA 11, SS 11). Additionally, 14 cases were anti-SS-A antibody (Ab) positive (positive for the Ab 2, SLE 6, SS 10). With regard to immunosuppressants and antirheumatic drugs, 1 case with AOSD had started tacrolimus, 2 cases (SLE 1 and AOSD 1) had continued the same prescription, and 8 cases (RA 5, SLE 2, MCTD 1) discontinued them. With regard to steroids, 13 cases (SLE 9, RA 3, AOSD 1) received increased dosages. With regard to fetal complications, a complete AV block was found in 1 case, whose mother was positive for anti-SS-A Ab. [Conclusion] This research broadly reflects a reality of pregnancy and childbirth management in a Japanese tertiary center with obstetrical and rheumatologic departments. Although some cases required reinforcement of the treatment, the data suggest that it is possible for cases with CD to experience a safe delivery.

## P2-007

### Differences in rheumatoid arthritis patients' profiles according to the reasons for not using Methotrexate

Hirota Tsuno<sup>1</sup>, Toshihiro Matsui<sup>1</sup>, Atsushi Kaneko<sup>2</sup>, Koichiro Saisho<sup>3</sup>, Hiroshi Kajiyama<sup>4</sup>, Toshihide Mimura<sup>4</sup>, Jinju Nishino<sup>5</sup>, Shigeto Tohma<sup>6</sup>

<sup>1</sup>Department of Rheumatology, Sagami National Hospital, National Hospital Organization, <sup>2</sup>Department of Orthopaedic Surgery, Nagoya Medical Center, NHO, <sup>3</sup>Department of Orthopaedic Surgery, Miyakonojo Hospital, NHO, <sup>4</sup>Department of Rheumatology and Applied Immunology Faculty of Medicine, Saitama Medical University, <sup>5</sup>Department of Orthopaedic Surgery, The University of Tokyo Hospital, <sup>6</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, National Hospital Organization

Conflict of interest: None

[Objective] To investigate differences in rheumatoid arthritis patients' profiles according to the reasons for not using Methotrexate. [Methods]

11940 patients registered in NinJa 2012 were divided into two groups: 7404 who take MTX (Group A) and 4536 who don't take MTX (Group B). The reasons for not taking MTX were apparent in 1360 patients of Group B. Within this group, MTX treatment was not necessary in 803 patients (Group B1) and was not suited in 557 patients (Group B2). We compared patients' backgrounds, disease activities, usage rates of biologics, DMARDs except for MTX, corticosteroid, and NSAIDs among these 4 groups. [Results] Renal function was lower in Group B especially in Group B2 than Group A. Disease activity (CDAI) in group B1 didn't show significant difference compared to group A. However, CDAI in group B2 was significantly higher than group A (10.0 vs. 7.4,  $p < 0.0001$ ). Usage rate of biologics was significantly higher in group B2 than group B1 (42.5% vs 16.2%,  $p < 0.0001$ ). Usage rates of steroid, SASP, BUC, NSAIDs were low in group B2 than group B1. [Conclusions] Renal failure was suggested to be one reason why MTX is unusable. Although usage rate of biologics is higher in group B2, the disease activity of the group is higher than other groups.

## P2-008

### Increase in age at onset of rheumatoid arthritis (RA) – Analysis based on NinJa database

Eri Kimura<sup>1</sup>, Tetsuji Sawada<sup>1</sup>, Koichiro Tahara<sup>1</sup>, Haeru Hayashi<sup>1</sup>, Mayu Tago<sup>1</sup>, Hiroaki Mori<sup>1</sup>, Toshihiro Matsui<sup>2</sup>, Jinju Nishino<sup>3</sup>, Shigeto Tohma<sup>2</sup>  
<sup>1</sup>Department of Rheumatology, Tokyo Medical University Hospital, Tokyo, Japan, <sup>2</sup>Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara National Hospital, Sagamihara, Japan, <sup>3</sup>Nishino Clinic, Orthopaedics and Rheumatology, Tokyo, Japan

Conflict of interest: None

[Objectives] The increase in age at onset of RA in Japan was reported by Imanaka et al, demonstrating the peak age to be shifted from 2nd to 4th decade from 1960 to 90. The purpose of the present study was to investigate the shift of RA onset age during the last 10 years using NinJa. [Methods] We analyzed the average age of early RA onset (within 2 years) using NinJa 2003, 2008 and 2013. Japan age structure was calculated using database from Bureau of General Affairs. [Results] The average onset age of early RA was significantly increased in NinJa 2003, 2008 and 2013 (55.7 57.0 and 59.9). The peak age was shifted from 5th (NinJa 2003) to 6th decade (NinJa 2013). Although the elderly population increased due to aging of 1st baby-boomers, elderly onset RA (after 70 years old) was disproportionately increased. The 4th decade population was maintained due to 2nd baby-boom, and RA development in 4th decade was not altered. Although elderly-onset RA was predominantly female (75%), which was similar during this period. [Conclusion] The age of RA onset was significantly increased, which may result from the change of environmental factors, or demographic change occurring (birth cohort phenomenon) during the last 10 years in Japan.

## P2-009

### Prevalence and factors associated with depression and anxiety in patients with rheumatoid arthritis – Analysis of NinJa 2013 database-

Masao Katayama<sup>1</sup>, Tomoya Miyamura<sup>2</sup>, Yasuo Suenaga<sup>3</sup>, Eiichi Suematsu<sup>2</sup>, Yukitomo Urata<sup>4</sup>, Jinju Nishino<sup>5</sup>, Toshihiro Matsui<sup>6</sup>, Shigeto Tohma<sup>7</sup>  
<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Nagoya Medical Center, National Hospital Organization, Nagoya, Japan, <sup>2</sup>Department of Internal Medicine and Rheumatology, Kyushu Medical Center, National Hospital Organization, Fukuoka, Japan, <sup>3</sup>Department of Rheumatology, Beppu Medical Center, National Hospital Organization, Oita, Japan, <sup>4</sup>Department of Rheumatology, Seihoku Central Hospital United Municipalities of Tsugaru, Aomori, Japan, <sup>5</sup>Department of Orthopaedic Surgery, University of Tokyo School of Medicine, Tokyo, Japan, <sup>6</sup>Department of Rheumatology, Sagamihara Hospital, National Hospital Organization, Sagamihara, Japan, <sup>7</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihara Hospital, National Hospital Organization, Sagamihara, Japan

Conflict of interest: None

[Objectives] To analyze the prevalence and factors associated with depression and anxiety in RA patients using data from a large Japanese

cohort database. [Methods] The 7,479 patients analyzed in this study were enrolled in NinJa database during the fiscal year of 2013 with results from the Hospital Anxiety and Depression Scale (HADS). Differences in clinical data were analyzed between a depression group (DG) with score  $\geq 11$  and non-DG with score  $< 10$ . As is for anxiety. [Results] The frequency of DG was 9.2% and that of AG 7.0%. Mean age was significantly higher in DG and AG than in non-DG and non-AG. In addition, DG and AG showed significantly longer disease duration, higher mHAQ score and higher disease activity. Multivariate analyses identified mHAQ as factors independently associated with DG ( $p < 0.001$ , OR 1.870, 95% CI 1.492-2.344). Work state and age were observed as negative factors for DG. Likewise, mHAQ and female sex were observed as independently associated with AG ( $p < 0.001$ , OR 2.297, 95% CI 1.796-2.939 and  $p < 0.005$ , OR 1.795, 95% CI 1.281-2.516, respectively). [Conclusion] This study examined the prevalence of two important constructs, depression and anxiety, in Japanese RA patients. It is suggested that anxiety should be considered as a distinct construct in RA patients.

## P2-010

### The effect of anti-IL-6 receptor antibody on the deterioration in bone structure in a mouse model of collagen-induced arthritis

Hiroto Yoshida, Miho Suzuki, Keisuke Tanaka, Misato Hashizume, Yoshihiro Matsumoto  
Product Research Department, Chugai Pharmaceutical Co., Ltd.

Conflict of interest: None

[Objectives] RA is a disease that typically induces secondary osteoporosis. Bone fracture is induced not only by lower BMD but also by deterioration in bone structure. We examined how bone structure was affected by anti-IL-6 receptor antibody in CIA mice. [Methods] CIA mice were injected intraperitoneally with anti-mouse IL-6 receptor antibody (MR16-1) on Days 0 and 21. Urinary CTX and serum PINP on Day 35 were measured by ELISA. In the distal femur and L5 lumbar spine, the bone structure on Day 56 was analysed by  $\mu$ CT. [Results] In CIA mice, CTX and PINP were significantly higher and lower, respectively, than in non-immunized mice. Trabecular bone volume (BV/TV), trabecular number (Tb.N), trabecular thickness (Tb.Th), and cortical bone thickness (Ct) of the femur, and BV/TV and Tb.N of the lumbar spine in CIA mice were significantly lower than in non-immunized mice. An increase in CTX and a decrease in PINP during development of CIA were prevented by MR16-1. MR16-1 treatment significantly suppressed the deterioration in bone structure (BV/TV, Tb.N, Tb.Th, and Ct in the femur, and BV/TV and Ct in the lumbar spine). [Conclusion] Our findings indicate that anti-IL-6 receptor antibody improves the imbalance in bone turnover and thus prevents the deterioration in bone structure.

## P2-011

### Suppressive ability of altered peptide ligand transgenic rice against glucose-6-phosphate isomerase peptide induced arthritis

Tomoya Hirota, Hiroto Tsuboi, Mana Iizuka, Hiroyuki Takahashi, Hiromitsu Asashima, Isao Matsumoto, Takayuki Sumida  
Department of Internal Medicine, Faculty of Medicine, University of Tsukuba

Conflict of interest: None

[Objectives] To reveal the suppressive effect of altered peptide ligand (APL) transgenic rice against glucose-6-phosphate isomerase (GPI) peptide induced arthritis model mouse (pGIA). [Methods] We designed APL construct containing T cell epitopes (AA325-339) of GPI peptide, in which one amino acid in T cell binding sites was substituted, with conserved anchor motif for binding to MHC class II molecules, and then generated APL construct transgenic rice. Before immunization with GPI peptide, APL transgenic rice (APL group) or non-transgenic rice (control group) was orally administered to pGIA for 7 days (-day7~day1). 1) Severity of arthritis, 2) cytokine production in draining lymph nodes (dLN) (day28), and 3) histopathological analysis of ankle joints (day28) were evaluated. [Results] 1) Severity of arthritis was significantly suppressed in APL group at day 10, 20 and 22 compared to control group (Scores at day 20: APL 4.0 $\pm$ 1.4, control 7.3 $\pm$ 1.4,  $P < 0.05$ ). 2) IFN $\gamma$  and IL-17 productions from dLN cells after stimulation with GPI peptide were compa-

rable between APL and control groups (N.S) 3) Synovitis and bone erosion in ankle joints were similar between APL and control groups (N.S). [Conclusion] Oral prophylactic treatment with APL of GPI peptide transgenic rice might suppress severity of pGIA.

## P2-012

### Preventive and therapeutic effects of anti-IL-6 receptor antibody on spontaneously occurring rheumatoid arthritis in an Fc $\gamma$ RIIB-deficient mouse model

Mareki Ohtsuji<sup>1,2</sup>, Qingshun Lin<sup>1</sup>, Keiko Nishikawa<sup>1</sup>, Hideki Okazaki<sup>3</sup>, Hirofumi Amano<sup>4</sup>, Hiroyuki Nishimura<sup>1,2</sup>, Norihiro Nishimoto<sup>5</sup>, Toshikazu Shirai<sup>1</sup>, Sachiko Hirose<sup>1</sup>

<sup>1</sup>Department of Pathology, Juntendo University School of Medicine, <sup>2</sup>Toin Human Science and Technology Center, Department of Biomedical Engineering, Toin University of Yokohama, <sup>3</sup>Health and Life Science, Musashigaoka Junior College, <sup>4</sup>Department of Internal Medicine, Juntendo University School of Medicine, <sup>5</sup>Osaka Rheumatology Clinic

Conflict of interest: None

[Objectives] To examine the preventive and therapeutic effects of anti-IL-6 receptor (IL-6R) mAb (MR16-1) on spontaneously occurring rheumatoid arthritis-like disease in arthritis-prone Fc $\gamma$ RIIB-deficient B6 mice, designated KO1. [Methods] The preventive effect was examined by treating 4-mo-old preclinical KO1 mice for 6 months, and the therapeutic effect was by treating 7-mo-old KO1 mice in the early stages of arthritis for 2 months. The severity of arthritis and transcription levels of several arthritis-related factors in ankle joint tissues were compared with the control mice. [Results] The preventive treatment markedly suppressed the arthritis with the significant suppression of transcription levels of MCP-1 and TNF $\alpha$  and RANKL/OPG ratio in ankle joints. However, ROR $\gamma$ t and Foxp3 levels were not affected. In the therapeutic treatment, the disease progression was suppressed with the reduced expression of MCP-1 and the decreased RANKL/OPG ratio, but TNF $\alpha$  expression level was not suppressed. [Conclusion] The suppression of arthritis by MR16-1 was associated with the decrease in RANKL/OPG ratio, but not Treg/Th17 balance in KO1 mice. The earlier treatment is the more effective to suppress TNF $\alpha$  expression in arthritic lesion.

## P2-013

### Effects of Fc $\gamma$ RIIB deficiency, *Slam* haplotype and *Yaa* mutation on the pathogenesis of SLE

Keiko Nishikawa<sup>1</sup>, Qingshun Lin<sup>1</sup>, Hirofumi Amano<sup>2</sup>, Hiroyuki Nishimura<sup>3</sup>, Toshikazu Shirai<sup>1</sup>, Sachiko Hirose<sup>1</sup>

<sup>1</sup>Department of Pathology, Juntendo University School of Medicine, <sup>2</sup>Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, <sup>3</sup>Toin Human Science and Technology Center, Department of Biomedical Engineering, Toin University of Yokohama

Conflict of interest: None

[Objectives] We examined the role of Fc $\gamma$ RIIB deficiency, autoimmune-type *Slam*<sup>129</sup> haplotype, and *Yaa* with TLR7-duplication for the pathogenesis of SLE. [Methods] Three mouse strains carrying Fc $\gamma$ RIIB deficiency alone, *Slam*<sup>129</sup> haplotype alone, or both of them, were established in B6 genetic background, and introduced with *Yaa*. Disease phenotypes in these mice were examined along with those in B6 and B6.*Yaa* mice. [Results] Mice carrying only Fc $\gamma$ RIIB deficiency, *Slam*<sup>129</sup>, or *Yaa* seldom developed any autoimmune phenotypes. Mice carrying Fc $\gamma$ RIIB deficiency and *Slam*<sup>129</sup> developed RA-like arthritis; however, the disease phenotype was converted from RA to SLE by *Yaa* introduction. Mice carrying Fc $\gamma$ RIIB deficiency and *Yaa*, and carrying *Slam*<sup>129</sup> and *Yaa* developed SLE, but the disease was more severe in the former than in the latter. [Conclusion] A single susceptible gene was not enough for the development of SLE, and the combination of more genes induced more severe disease. The introduction of *Yaa* accelerates SLE in combination with Fc $\gamma$ RIIB deficiency and *Slam*<sup>129</sup>; however, Fc $\gamma$ RIIB deficiency showed the more effective than *Slam*<sup>129</sup>. This may be due to the fact that Fc $\gamma$ RIIB deficiency and *Yaa* both contribute to B cell activation, resulting in easily lowering the threshold of auto-reactivity of B cells.

## P2-014

### The expression of the oxytocin-monomeric red fluorescent protein 1 (mRFP1) fusion gene in the hypothalamus and spinal cord of acute nociceptive model rats

Takanori Matsuura<sup>1,2</sup>, Makoto Kawasaki<sup>2</sup>, Yasuhito Motojima<sup>1,2</sup>, Hitoshi Suzuki<sup>2</sup>, Hideo Ohnishi<sup>2</sup>, Yoichi Ueta<sup>1</sup>

<sup>1</sup>Department of Physiology, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, <sup>2</sup>Department of Orthopaedics, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

Conflict of interest: None

[Objectives] Oxytocin (OXT) is a well-known neurohypophysial hormone that is synthesized in the paraventricular (PVN) and the supra-optic nuclei (SON) of the hypothalamus. Several lines of evidence have suggested that OXT plays an important role in pain modulation and analgesia. However, it is unknown about the neuronal spinal networks responsible for OXT effects. [Methods] The present study examined the effects of acute nociceptive stress on the expression of the OXT-monomeric red fluorescent protein 1 (mRFP1) fusion gene in the hypothalamus and spinal cord of the transgenic rats. As the acute nociceptive model, OXT-mRFP1 transgenic rats were subcutaneously injected with formalin at the bilateral hindpaws. We observed mRFP1 fluorescence in the PVN, the SON and the dorsal horn in the spinal cord after formalin injection. The expression levels of the mRFP1 and the OXT gene in the hypothalamus were also measured by *in situ* hybridization histochemistry. [Results] We revealed that mRFP1 and OXT mRNA levels in the PVN and the SON, and the mRFP1 fluorescence in the dorsal horn were significantly increased at 2 hour after formalin injection compared with controls. [Conclusion] Increased hypothalamic OXT may associate with spinal pathway and influence mechanical nociceptive threshold.

## P2-015

### Increased Sec61 in endosome facilitates antigen cross-presentation and induces immune glomerular injury

Ken Tsumiyama, Shunichi Shiozawa  
Department of Medicine, Rheumatic Disease Unit, Kyushu University Beppu Hospital, Beppu, Japan

Conflict of interest: None

[Objectives] We found that SLE was induced by repeatedly immunizing the mice with antigen, and have proposed a novel 'self-organized criticality theory' explaining the cause of SLE. Cytotoxic T lymphocyte (CTL) generated *via* antigen cross-presentation induces lupus tissue injuries. Here we examine the molecular mechanism of antigen cross-presentation in relation to lupus nephritis. [Methods] Bone marrow-derived DC (BMDC) was cultured with ovalbumin (OVA) and/or an inhibitor of Sec61 Exotoxin A. Sec61 was immunoprecipitated from BMDC, followed by detection of OVA. OVA in cytoplasm was also detected. Mice were repeatedly immunized with OVA to induce SLE. Sec61 in endosome of splenic DC (spDC) was detected using immunoprecipitation of EEA1, followed by detection of Sec61. Further, OVA in cytoplasm was detected. [Results] In BMDC, OVA was co-precipitated with Sec61. OVA was detected in cytoplasm of BMDC, however, Exotoxin A abolished the detection of OVA. In spDC of mice developed glomerular injury, not only Sec61 in endosome but also OVA in cytoplasm were increased. [Conclusion] Antigen is exported directly from endosome to cytoplasm *via* Sec61. Increase of Sec61 in endosome promotes antigen cross-presentation and is an essential for the development of glomerular injury likely of SLE.

## P2-016

### The impact of biologics on the titer of autoimmunity in established rheumatoid arthritis patients -from Airtight Study-

Shohei Anno<sup>1,4</sup>, Kenji Mamoto<sup>2</sup>, Tadashi Okano<sup>2,3</sup>, Yuko Sugioka<sup>2</sup>, Masahiro Tada<sup>2</sup>, Kentaro Inui<sup>2</sup>, Tatsuya Koike<sup>1,3,4</sup>

<sup>1</sup>Shirahama Hamayu Hospital, Wakayama, Japan, <sup>2</sup>Dept. of Orthopedic Surgery, Osaka City University Medical School, Osaka, Japan, <sup>3</sup>Center for Senile Degenerative Disorder, Osaka City University Medical School, Osaka, Japan, <sup>4</sup>Serch Institute for Bone and Arthritis Disease, Wakayama,

Japan

Conflict of interest: None

[Objective] We assessed the impact of biologics on the titer of autoimmunity in established rheumatoid arthritis patients (RA) in the Airtight study. [Method] 107 patients (mean age 60±14.1 years, mean duration of disease 10.2, MTX use 81.7%) with RA started biologics treatment. 31 patients were treated with abatacept (ABT), 58 patients with anti tumor necrosis factor inhibitors (aTNF), 18 patients with tocilizuma (TOC). The titers of antibodies against cyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF) and autoantibody to galactose deficient IgG (CA-RF) were measured at baseline and 48 week after treatment. [Result] The titers of anti-CCP at baseline was 143.4±181.7U/ml in ABT, 158.2±153.2 in aTNF, 148.7±164.8 in TOC, and after 48 week treatment were 139.9±170 in ABT, 128.9±150.3 in aTNF, 97.9±153.2 in TOC. Both baseline and after treatment, there were no significant difference among the three groups by analysis of variance. The changes in aTNF and TOC were a little greater than that of ABT by non-parametric multiple comparison (p=0.06). The changes of RF and CA-RF were comparable result. [Conclusion] It suggest that the titer of anti-CCP decrease during treatment with biologics in established RA, but the impact of biologics differ according to the type of biologics.

## P2-018

### Relationship between the titre of anti-ARS antibody and clinical feature

Kenichiro Hata, Kentaro Isoda, Katsuhiko Oda, Yuki Yoshimatsu, Ipppei Morimoto  
Yodogawa Christian Hospital

Conflict of interest: None

Objective: To investigate the relationship the titer of anti-ARS antibody and clinical feature. Methods: We assessed 113 patients who were examined anti-ARS antibody for the purpose of screening of connective tissue disease or interstitial lung disease. They were divided into 3 groups by the titer of anti-ARS antibody.: Group A was defined as anti-ARS antibody positive (> 25), the titer of Group B was less than measurement sensitivity (< 5) and the titer of Group C ranged from 5 to 25. Result: The mean age was 60.3 ± 15.5 years old. Forty three cases had interstitial lung disease (ILD). Six, ninety three and fourteen cases belonged to Group A, Group B and Group C respectively. Three of seven DM/PM patients were anti-ARS antibody positive. The frequency of ILD was 83.3%, 30.1% and 76.9% in Group A, B and C respectively. There was a significant difference in the frequency of ILD between Group A or C and Group B (p=0.0191, p=0.0039). Conclusion: When the titer of anti-ARS antibody is more than 5, ILD is often complicated.

## P2-019

### Relationship between congenital heart block (CHB) and the maternal serological titer of anti-SS-A antibody subtype

Mikako Goto, Kayoko Kaneko, Atsuko Murashima  
Division of Maternal Medicine, Center of Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, Tokyo, Japan

Conflict of interest: None

[Objectives] Fetuses of the mother with anti SS-A/Ro Ab are at risk of developing CHB. There are some studies that anti 50kDa-Ab has association with CHB of their offspring, it is still in controversial. Here we have validated in our own experience. [Methods] Fifty-one pregnant patients, who have attended to our division during 2002 to 2011, and whose consequential child's health is known, were analyzed. Patients' characteristics and serological titers of anti 52kDa-Ab and anti 60kDa-Ab were measured using commercial ELISA kit (MESACUP, MBL). Wilcoxon rank-sum test was used to analyze the relationship between the titer and occurrence of CHB. [Results] Median age of mother was 34 (range 27-43), and 18 fetus developed CHB. Thirty-four cases were diagnosed as autoimmune diseases. Median titer of anti 52kDa Ab was 148.8 (11.5-177.3) and 64.4 (0-206.3), and that of anti 60kDa Ab was 99.1 (10.4-

178.8) and 20.3 (0.2-229.3) in mother with CHB developed and undeveloped fetus, respectively. Relationship between titer of Ab and development of CHB in child was only statistically significant in anti 60kDa-Ab. [Conclusion] In contradiction to the previous reports, only the titer of maternal anti 60kDa-Ab and not anti 50kDa-Ab has associated with the development of CHB.

## P2-020

### Inhibitory activity of serum autoantibodies to ACE2 in patients with constrictive rheumatic vasculopathies, using angiotensin (1-7) assay

Yuko Takahashi<sup>1</sup>, Shiori Haga<sup>2</sup>, Yukihito Ishizaka<sup>3</sup>, Akio Mimori<sup>1</sup>  
<sup>1</sup>Division of Rheumatic Diseases, National Center for Global Health and Medicine, <sup>2</sup>Department of Intractable Diseases, Research Institute, National Center for Global Health and Medicine

Conflict of interest: None

[Objectives] We have reported inhibitory serum autoantibodies (Ab) to angiotensin2 (ACE2) in patients with rheumatic diseases and pulmonary arterial hypertension (PAH) or digital necrosis, and non-inhibitory antibodies to ACE2 in active SLE patients. This study presents a sensitive method for detecting anti-ACE2 inhibitory Ab, which measures physiological substrate AngII and the product Ang (1-7) by High performance liquid chromatography (HPLC). [Methods] Serum IgG fraction was obtained from 29 SLE patients (4 PAH, 2 digital necrosis, 19 active SLE without vasculopathy, 4 and control SLE) and one patient with Sjogren syndrome and PAH. After co-incubation of ACE2 and AngII with patient's IgG, Ang (1-7)/AngII-ratios were estimated. [Results] ACE2 inhibition by serum IgG was shown in 4/5 of PAH, 2/2 of digital necrosis, and 3/19 of active SLE without vasculopathy (6/7 vs 3/19; p = 0.0022), and none of 4 controls. The in vitro ACE2 inhibition by the IgG from a Sjogren-PAH patient was diminished after steroid therapy, which treated the PAH successfully. [Conclusion] Ang (1-7)/AngII assay by HPLC may be a sensitive method for detecting inhibitory autoantibodies to ACE2 in rheumatic vasculopathy.

## P2-021

### Autoantibodies to Ki/SL antigen (PA28γ) in systemic rheumatic diseases in the United States

Shin Tanaka<sup>1</sup>, Monika Gonzalez<sup>2</sup>, Yi Li<sup>2</sup>, Westley H. Reeves<sup>2</sup>, Michael R. Bubb<sup>2</sup>, Mark Segal<sup>2</sup>, S. John Calise<sup>3</sup>, Edward K.L. Chan<sup>3</sup>, Eric S. Sobel<sup>2</sup>, Minoru Satoh<sup>4</sup>

<sup>1</sup>Department of Human Information and Life Sciences, School of Health Sciences, University of Occupational and Environmental Health, Kitakyushu, Japan, <sup>2</sup>Department of Medicine, University of Florida, Gainesville, FL, USA, <sup>3</sup>Department of Oral Biology, University of Florida, Gainesville, USA, <sup>4</sup>Department of Clinical Nursing, School of Health Sciences, University of Occupational and Environmental Health, Kitakyushu, Japan

Conflict of interest: None

[Objectives] Anti-Ki/SL antibodies that recognize proteasome activator 28γ(PA28γ) have been reported in ~10% of SLE patients in Japan and a few European countries but there are no data available from U.S. Anti-Ki/SL antibodies in a U.S. rheumatology cohort was examined and their clinical association analyzed. [Methods] Unselected patients from U.S. rheumatology clinic under diagnoses of SLE (n=462), SSc (n=125), RA (n=138), PM/DM (n=132), or Sjögren's syndrome, (SS, n=63) were studied. Sera from patients and controls (NHS, n=60) were screened for anti-Ki/SL antibodies by immunoprecipitation (IP) and by ELISA. ELISA-positive sera were confirmed by IP-western blot. Immunofluorescence antinuclear/cytoplasmic antibodies were tested using HEP-2 cells. [Results] Anti-Ki/SL antibodies were detected in SLE (32/462, 6.9%) and SSc (3/125, 2.4%). In SLE, prevalence of the antibodies in Latin (18.8%) was significantly higher vs Caucasian (5.4%, p = 0.0044) or African American (6.4%, p=0.019). Photosensitivity (p=0.06), psychosis (p=0.10), and anti-dsDNA antibodies (p=0.03) were more prevalent in anti-Ki/SL (+). Anti-Ki/SL (+) sera typically showed fine-speckled nuclear staining pattern. [Conclusion] Anti-Ki/SL antibodies were detected in SLE and SSc, in particular Latin SLE patients in U.S.



## P2-022

### Association with auto-antibodies on vascular endothelial cells and patient with Raynaud' phenomenon

Souichiro Nakano<sup>1,2</sup>, Satoshi Suzuki<sup>1,2</sup>, Kenjiro Yamanaka<sup>2</sup>, Yoshinari Takasaki<sup>1</sup>

<sup>1</sup>Department of Rheumatology and Internal Medicine, Juntendo University School of Medicine Tokyo, Japan, <sup>2</sup>Sasaki Institute, Sasaki Foundation, Tokyo, Japan

Conflict of interest: None

[Objectives] We investigated that association with auto-antibodies on vascular endothelial cells and Raynaud' phenomenon from systemic autoimmune disease. [Methods] We obtained peripheral blood from 3 patients with SSc, 4 with SLE, 5 with RA and 6 healthy controls, and assessed the numbers of endothelial progenitor cells by FCM. Next, we performed immune-blot analysis on vascular endothelial cell lysate from patient with Raynaud' phenomenon. [Results] The numbers of endothelial progenitor cells in patient with Raynaud' phenomenon was significant decreased than in other patients and healthy controls. Anti-endothelial cell antibody and Anti-endothelin B receptor antibody was performed from patient with Raynaud' phenomenon. [Conclusion] Our result suggest that auto-antibodies on vascular endothelial cell is exerted the role of Raynaud' phenomenon.

## P2-023

### Study about relation of blood flow signal in musculoskeletal ultrasound and Quality of Life in rheumatoid arthritis patient

Ryo Yanai, Hidekazu Furuya, Yusuke Miwa, Kuninobu Wakabayashi, Sakiko Isojima, Masayu Umemura, Nao Oguro, Sho Ishii, Shinya Seki, Tsuyoshi Kasama

Division of Rheumatology, Department of Medicine, Showa University of Medicine, Tokyo, Japan

Conflict of interest: None

**Purpose** Then correlation of blood flow signal of MSUS and HAQ in RA patient was examined. **Method** 29 RA patients were targeted by Sep 2014 from Sep 2013, and start of biological preparation or the change was conducted. HAQ and MSUS were conducted before at the time of start or the change. MSUS was conducted with both joints of total 34 of MCP, PIP, hand, knee, MTP, and presence of blood flow signal was confirmed. It was divided into the following points, and each HAQ was weighed. (1) Control which blood flow is seen in MCP or PIP joint of both sides and control which are not seen, (2) In knee or MTP joint of both sides and control (3) In either of carpal joint of both sides and control **Fructification** As a result of having compared it, significant difference was not recognized entirely so that the following fructification showed it. 1.11 (N=13) vs. 0.76 (N=26) (P = 0.28), 0.88 (N=13) vs. 0.85 (N=26) (P = 0.03), 0.83 (N=22) vs. 1.18 (N=7) (P = 0.36), **Conclusive words** The correlation was not found between presence of the blood flow signal and HAQ. It is assumed that HAQ is affected by joint transformation for disease to be complicated, contraction of a disease period. HAQ is important index of QOL. However, the possibility that medical degree of synovitis may not be shown was suggested.

## P2-024

### Immediately evaluation of power doppler ultrasonography (PD) after the intravenous biologic (iBio) in Bio naïve Rheumatoid Arthritis (RA)

Soichiro Tsuji<sup>1</sup>, Takashi Shimizu<sup>1</sup>, Takuro Nii<sup>1</sup>, Akiko Yura<sup>1</sup>, Satoru Teshigawara<sup>1</sup>, Maiko Yoshimura<sup>1</sup>, Eriko Tanaka<sup>1</sup>, Yoshinori Harada<sup>1</sup>, Masato Matsushita<sup>1</sup>, Shiro Ohshima<sup>2</sup>, Jun Hashimoto<sup>1</sup>, Yukihiko Saeki<sup>2</sup>

<sup>1</sup>Department of Rheumatology and Allergology, Osaka Minami Medical Center, <sup>2</sup>Department of Clinical Research, Osaka Minami Medical Center

Conflict of interest: None

**OBJECTIVE** To investigate the therapeutic efficacy of iBio in Bio naïve RA by PD before and immediately after iBio evaluation of change in the wrist and hand, and to predict disease activity after 6 months. **METHODS** 9 RA who received iBio were examined by PD before and

immediately after iBio at baseline (BL). The patients DAS28ESR assessments were recorded at BL and 1, 3, 6 months. PD examinations of 22 joints were graded semi-quantitatively on a scale of 0-3. The PD scores were the sums of the PD signal scores (total PD; tPDs). We measured PD positive synovial sites immediately after iBio again. We evaluated the significance of tPDs by comparing it with before and immediately after iBio. Pre and Post-tPDs were assessed and divided into two groups: decreased tPDs (D group) and non-decreased (ND) group. Disease activities in the two groups were compared. The case of therapy intensification was recorded by LOCF. **RESULTS** tPDs were decreased in 4 RA (D group). 5 RA did not have decreased (ND group). Cases that have reached less than low disease activity were 2 RA (50%) for D group and 1 RA (20%) for ND group at 6 months. LOCF were 1 RA (25%) for D group, 4 RA (80%) for ND group. **CONCLUSION** Assessments of immediate tPDs at BL may predict the responses and refractory after 6 months.

## P2-025

### Study on usefulness of ultrasound in patients administered with biological-DMARDs

Kentaro Minowa, Michihiro Ogasawara, Misa Gorai, Yuko Matsuki, Yusuke Yamada, Nagachika Sugisaki, Takuya Nemoto, Seiichiro Ando, Takayuki Kon, Ken Yamaji, Naoto Tamura, Yoshinari Takasaki

Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Purpose] The examination of usefulness of ultrasound (US) on rheumatoid arthritis (RA) patients who administered with biological-DMARDs (Bio). [Method] We have used 25 patients who are capable to be administered with Bio for 52 weeks continuously. At 0, 12, 24 and 52th week, we have evaluated DAS28-ESR (4) and performed US on the 40 joints. We also evaluated  $\Delta$ TSS at 0 week and 52th week. We examined the clinical findings (tenderness/swelling) and PD findings and followed up to 52th week. Then, we compared any relationships with  $\Delta$ TSS. Next, 0 weeks scores of total PD and DAS28ESR and their cumulative scores from 0 to 52 weeks were compared with RP and non RP groups. [Result] Sustained PD and clinical findings rose the risk of RP. The accuracy of RP prediction was increased by complementation of US. RP occurrences which PD and clinical findings disappeared to 8-12 weeks were reduced. There was no significant difference both total PD and DAS-28ESR between RP and non RP. In three months time after Bio stopped, PD remission cases had maintained the PD remission, non-remission cases had increased the total PD scores. [Conclusion] Sustained PD undergoing Bio therapy showed risk of RP regardless of improvement of DAS. The confirmation of PD remission is desirable before trying the rest of Bio.

## P2-026

### Assessment of Synovial Inflammation by Superb Microvascular Imaging (SMI) in Patients with Rheumatic Disease

Kazuhiro Yokota, Takuma Wada, Yuji Akiyama, Toshihide Mimura

Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Saitama, Japan

Conflict of interest: None

[Objectives] To assess the efficacy of Superb Microvascular Imaging (SMI) in detecting synovial power Doppler (PD) signal in patients with rheumatic disease compared with conventional PD ultrasound (US). [Methods] Eleven patients with RA and 9 patients with non-RA patients were enrolled. We assessed PD signals in 26 bilateral finger, hand, elbow, and knee joints by the PDUS and SMI findings using Aplio 300 (Toshiba Medical Systems). The signals were semiquantified into 4 grades (0-3), with the total as the total PD scores. The correlation of the total PD scores with serum MMP-3 levels and SDAI in RA patients were determined. [Results] In patients with RA, the total PD scores detected on SMI were higher than those on PDUS (mean, 6.7 vs. 11.0; p = 0.06). In patients with non-RA, the scores had no significant difference (0.33 vs. 0.67, p = 0.24). The total PD scores detected on SMI had a stronger correlation to the serum levels of MMP-3 than those on the PDUS in patients with RA (r = 0.45 vs. r = 0.26). The SDAI also showed similar trends

(PDUS:  $r = 0.46$ , SMI:  $r = 0.57$ ). [Conclusion] Although future studies with more patients are needed, our data suggest that SMI might detect synovial PD signals more sensitively than conventional PDUS in patients with RA.

## P2-027

### Study of the association between ultrasonography and disease activity in systemic lupus erythematosus patients with arthralgia

Yuko Kimura, Shuzo Yoshida, Ayaka Yoshikawa, Yuri Hiramatsu, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa

Department of the Internal Medicine (I), Osaka Medical College, Osaka, Japan

Conflict of interest: None

[Objectives] We studied of the prevalence of inflammatory abnormalities of joints, tendons and ligaments in SLE by US. [Methods] We performed US for both sides of MCP, PIP, IP, wrist, elbow, shoulder, knee, ankle, and MTP joints, and extensor/flexor tendons in 25 cases with arthralgia among SLE. Gray Scale (USGS) and Power Doppler (USPD) images were graded semiquantitatively (scale 0 to 3). We classified USGS $\geq 2$  as USGS-positive (USGS<sub>p</sub>) and USPD $\geq 1$  as USPD-positive (USPD<sub>p</sub>). We judged a case with both synovium thickening/synovial fluid retention and USPD positive as inflammation of a tendon and its enveloping sheath. [Results] All cases met SLE clinical diagnostic criteria. 8 cases are anti CCP antibody positive (32%) and 12 case were anti SS-A antibody positive (48%). Twelve cases (48%) had no medication and 11 case (44%) had received PSL. We found USGS<sub>p</sub> of 24 cases (96%), USPD<sub>p</sub> of 18 cases (72%) and inflammation of a tendon/tendon sheath synovium of 18 cases (72%). USGS<sub>p</sub> in wrists of 20 cases (80%), MCPs of 17cases (68%), USPD<sub>p</sub> in wrists of 14 cases (56%), and MCPs and knees of 6 cases (24%), and inflammation of tendon/ tendon sheath synovium were found in fingers and wrists of 7 cases (28%). [Conclusion] We found inflammatory abnormalities of fingers and wrists by US in SLE patients with arthralgia.

## P2-028

### Influence of the Joint Damage of the Lower Extremities and the Upper Extremities on HAQ-DI in Patients with Rheumatoid Arthritis

Satoshi Nakazaki<sup>1</sup>, Takashi Murayama<sup>1</sup>, Shinichi Kato<sup>2</sup>

<sup>1</sup>Rheumatology, Johoku Hospital, Kanazawa, Japan, <sup>2</sup>Rheumatology, Kamiaraya Clinic, Kanazawa, Japan

Conflict of interest: None

[Objectives] To analyze correlations of the activities of daily living (ADL) with joint damage of upper and lower extremities in patients with RA. [Methods] The ADL of 118 female patients with RA under 69 years was assessed according to HAQ-DI. An erosion joints count (EJC) was defined as the number of joints  $\geq 2$  by Larsen scores of the whole body joints. These were divided into two parts by the upper extremities (shoulders, elbows, wrists, fingers) and the lower extremities (hips, knees, ankles, and feet). Multiple linear regression was used to identify factors affecting HAQ-DI. [Results] The mean HAQ-DI was 0.43, the mean upper ETC (UEJC) 4.3, the mean lower ETC (LEJC) 4.2. Fifty-one % patients received biologics, 68% patients methotrexate, and 18% patients prednisolone. Eighty-two % patients were in HAQ-DI remission ( $<0.5$ ). In multiple linear regression using LEJC, 38% of variance in HAQ-DI score could be explained. DAS28CRP explained 26%, LEJC 5%, RF 4%, prednisolone 2%, BMI 1%. In multiple linear regression using UEJC, 35% of variance in HAQ-DI score could be explained. But UEJC was not significant in this model. [Conclusion] HAQ-DI of female patients with RA had correlated more strongly LETC than UETC.

## P2-029

### Factors that influences speed of joint deformity in rheumatoid arthritis

Ichiro Yoshii

Yoshii Hospital from Medical Corporation Genyu

Conflict of interest: None

[Objectives] Joint deformity control is an important theme as well as disease activity control in rheumatoid arthritis (RA) treatment. We have investigated factors that make influence on speed of joint deformity. [Methods] 303 patients who had been treated more than 1 year have been analyzed in this study. From X-P in these patients, Sharp/van der Heijde Score (SHS) had measured, and its change is corrected as dSHS as one year change. Mean value of DAS28, SDAI, pain score, health assessment questionnaire, matrix metalloproteinase 3 in these period, age and SHS at baseline (AGE@BL and SHS@BL), term length from baseline to first clinical remission in DAS28 and SDAI (LR-DAS and LR-SDAI) were also calculated. Relationship between dSHS and each parameter have been evaluated statistically with linear regression test. The effect of biologics (BIO) was also evaluated statistically with Mann-Whitney U-test. [Results] Factors that have demonstrated significant close correlation with dSHS were LR-DAS and LR-SDAI. Significant factors that correlated negatively were AGE@BL, HAQ-DI, and SHS@BL. BIO demonstrated significant lesser dSHS. [Conclusion] As late as treatment start, as high as HAQ is, as progressed as SHS is, as quick as disease control does, the speed for joint deformity get slow.

## P2-030

### Six patients with primary SS have developed to active continuing arthritis (synovitis) indistinguishable from RA

Akira Sagawa

Sagawa Akira Rheumatology Clinic

Conflict of interest: None

**Background:** Sjogren's syndrome (SS) is an autoimmune disease and also belongs to a rheumatic disease. As one of the extraglandular symptom, SS sometimes shows arthralgia and arthritis, but rarely develops to destructive arthritis like RA. **Objective and Methods:** Six patients with primary SS in my clinic have developed to continuing arthritis (synovitis) indistinguishable from RA during the course of outpatient clinic. All of them showed active arthritis (synovitis) by Power Doppler ultrasonography (PDUS) and MRI method. Duration between the onset of SS and arthritis is from 8 years to 22 years (average 14.8 years). Long time has been needed to develop arthritis for these SS patients. At least 2 patients of them developed to true RA who went to under treatment with MTX. But in these two patients active arthritis (synovitis) has been still continuing. Drastic treatment may be needed in these cases. **Conclusion:** These states which is developing to continuous active arthritis in SS patients is rare. Mechanisms and the reasons of these states are unknown for now. But this should be elucidated by the study of collecting many similar Japanese cases in near future.

## P2-031

### Relationship between diurnal variation of the symptoms and joint ultrasonography findings in rheumatoid arthritis

Shinkai Ri, Tetsu Itami, Kenji Sakai, Asuka Inoue, Chiemi Tasaki, Kayo Asato, Toshihiko Shiga, Tomohiro Yano, Shoichi Hino, Kazuya Kishimoto, Yasuaki Nagare, Yuji Nozaki, Masanori Funauuchi, Itaru Matsumura

Department of Hematology and Rheumatology, Kinki University School Faculty of Medicine, Osaka, Japan

Conflict of interest: None

[Objectives] In rheumatoid arthritis (RA), there may be a diurnal variation like morning stiffness. Although it has been frequently used in the diagnosis and management of RA, diurnal variation in the joint ultrasonography (US) findings has not been reported. Here joint US performed in the morning and afternoon, and compared with clinical symptoms. [Methods] Sixteen patients with RA (average age; 61.1-year-old, male-female ratio; 1:3, disease duration; 7.1 years, DAS-CRP; 3.5) hospitalized for biological treatment, from 2012 to 2014 were assessed. We evaluate tender joint count (TJC), swollen joint count (SJC), patient VAS (Pt-VAS) in the morning and afternoon (at AM 10:00 and PM 4:00). We also evaluate GS-PD for 4 stages (0-3) in both finger, wrist, knee joints, and GS-PD for qualitative assessment (0,1) in both wrist joints' extensor thecal synovial membrane, elbow and shoulder joints' synovial membrane by joint US images for total GS-PD score (0-128). [Results] There

are no significant difference in the joint US findings, tender and swollen joint count, Pt-VAS and morning stiffness between the morning and afternoon. There are no changes in clinical and laboratory findings by time. [Conclusion] There were no significant diurnal changes in the disease activity scores or US findings.

## P2-032

### Usefulness of the Ultrasonography in osteoarthritis of the hand

Ikuko Onishi<sup>1</sup>, Masayuki Inoo<sup>1</sup>, Chie Takashima<sup>1</sup>, Yoshihiro Akashi<sup>2</sup>, Satoshi Tohdo<sup>1</sup>, Noriyuki Kurata<sup>2</sup>

<sup>1</sup>Utazuha Clinic, <sup>2</sup>Utazu Clinic

Conflict of interest: None

[Objectives] To evaluate the usefulness in osteoarthritis who have the symptom not only PIP joints but also MCP joints. [Methods] We underwent gray-scale (GS) and power Doppler (PD) ultrasonography at 10 fingers and bilateral wrists (22 joint) in 15 patients with osteoarthritis (OA) and 20 patients rheumatoid arthritis (RA) who had clinical symptom in PIP and MCP joints. Each joint was scored for synovial hypertrophy (GS), power Doppler (PD), bone erosion, tendinitis, teno-synovitis, and synovial fluid in the finger and wrist joints. [Results] 1) In PIP joints of OA, the synovial fluid were tend to more amount and clear than RA. 2) PD in PIP joints of OA was located at periphery of the osteophytes and surface of the proximal phalanx. 30% patients of OA had PD grade  $\geq 2$  in PIP joints, and 40% patients had GS grade  $\geq 2$ . Peritendinitis and desmitis were seen in some joints. 3) MCP joints in OA, some patients had PD in extra-articular space. Moreover, peritendinitis or tenosynovitis was also seen. [Conclusion] In some reports, PD grade  $\geq 2$  in PIP joints was more likely RA. But in OA patients who have strong inflammation, we can see high PD grade in the PIP joints and peritendon. It is significant to accumulate a case and to examine the picture feature of the case which should be treated.

## P2-033

### DNA microarray analysis of resistin-induced gene expression on rheumatoid synovial fibroblast

Hiroshi Sato, Sei Muraoka, Shotaro Masuoka, Mai Kawazoe, Emiko Shindo, Natsuki Fujio, Kotaro Shikano, Makoto Kaburaki, Nahoko Tanaka, Kaichi Kaneko, Tatsuhiro Yamamoto, Natsuko Kusunoki, Tomoko Hasunuma, Shinichi Kawai

Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Toho University

Conflict of interest: None

[Objectives] We have previously reported that serum resistin level was significantly higher in rheumatoid arthritis (RA) patients. Accordingly, the aim of this study is to determine the direct effects of resistin on rheumatoid synovial fibroblasts (RSFs). [Methods] Synovial tissues were obtained from RA patients who were undergoing joint replacement surgery. RSFs harvested from the synovial tissues, were treated for 18h with various concentrations of resistin. Then, total RNA was extracted from the cells and the gene expression profile of RSFs was analyzed by DNA microarray. To confirm the result of microarray analysis, RT-PCR was performed. [Results] Microarray analysis revealed that resistin up-regulated expression ( $\geq 3.0$  fold change) of 45 genes on RSFs, including chemokines, inflammatory cytokines, receptors, receptor-related proteins, and adhesion molecules. These gene expressions were increased in concentration-dependent manners of resistin. Chemokines such as IL8, CXCL1, and CCL2 were markedly increased and their expressions were confirmed by RT-PCR respectively. [Conclusion] It is suggested that resistin might be a pro-inflammatory cytokine that up-regulates chemokine expressions in RSFs.

## P2-034

### Significance of Midkine in rheumatoid synovial fibroblasts

Emiko Shindo, Tomoko Hasunuma, Natsuko Kusunoki, Shotaro Masuoka, Mai Kawazoe, Hiroshi Sato, Natsuki Fujio, Kotaro Shikano, Makoto Kaburaki, Sei Muraoka, Tatsuhiro Yamamoto, Kaichi Kaneko, Kenji Takagi, Shinichi Kawai

Division of Rheumatology, Department of Internal Medicine, School of Medicine, Faculty of Medicine, Toho University

Conflict of interest: None

[Objectives] Midkine (MK) is a heparin-binding growth factor, which is known to be expressed in various solid tumors and considered to have an important role in tumor proliferation and invasion. MK also has various functions such as exacerbation of inflammation and tissue repair. Last year, we reported that serum MK level in rheumatoid arthritis (RA) patients was significantly increased compared to healthy controls. In this study, we examined MK expression in RA synovial fibroblasts (RSFs). [Methods] Immunohistochemical analysis was performed using RA and osteoarthritis (OA) synovial tissues, which were obtained at total knee replacement surgery in our hospital. MK mRNA expression in RSFs was also examined by RT-PCR, with and without stimulation by dexamethasone, interleukin 1 $\beta$ (IL-1 $\beta$ ) or tumor necrosis factor- $\alpha$ (TNF $\alpha$ ). [Results] MK protein was clearly detected in RA synovial lining layer compared to OA synovial tissue by immunohistochemical analysis. MK mRNA in RSFs was also detected, however, its expression levels did not change by stimulation with dexamethasone, IL-1 $\beta$ , or TNF $\alpha$ . [Conclusion] MK protein and mRNA were expressed in RSFs, but the mRNA expression was not changed by inflammatory cytokines or glucocorticoid stimulation.

## P2-035

### Arthroscopic Findings in Rheumatic Arthritis Cases Diagnosed as a result of Arthroscopic Surgery

Weijia Chen, Ryuji Nagamine

Joint Reconstruction and Rheumatic Center, Fukuoka Tokushukai Hospital

Conflict of interest: None

[Objectives] The arthroscopic findings were assessed in patients who had the chief complaint of gonalgia and were later diagnosed as RA through arthroscopic surgery. [Methods] From 2010, five cases were diagnosed as RA through arthroscopic surgery. The mean age was 58. The conditions of synovitis, cartilage, meniscus and ACL were observed and estimated. [Results] In all the cases, significant synovitis was recognized. ACL was covered with synovial membrane without loosening or damage. Mild to moderate fissure of joint cartilage; in some cases partially concaved or softened cartilage were also observed. Mild to moderate meniscus disorder was found in 3 cases, In which, the meniscus was not damaged but looked like to be in the early stage of erosion. The average MMP-3 data was 384ng/ml and was significantly high (1460ng/ml) in one case. Pre-operative radiography showed normal joint space was preserved in all the cases. Those findings suggested that even with a Larsen grade of 0-I, the MMP-3 was increased and the erosion of the joint cartilage and meniscus had started. [Conclusion] From these findings, it is apparent that the erosion of joint cartilage started from the early stage of RA. To achieve effective treatment, early intervention is necessary to prevent joint destruction.

## P2-036

### Decrease in the expressions of glycosylation related genes in the bone marrow cells from rheumatoid arthritis (RA) patients detected by DNA microarray analysis

Mari N Ito<sup>1,2</sup>, Miho Murakami<sup>1,2</sup>, Kensuke Ochi<sup>3</sup>, Yasunori Shimaoka<sup>4</sup>, Takahiro Ochi<sup>5</sup>, Norihiro Nishimoto<sup>1,2</sup>

<sup>1</sup>Department of Molecular Regulation for Intractable Diseases, Institute of Medical Science, Toyo Medical University, Tokyo, Japan, <sup>2</sup>Osaka Rheumatology Clinic, <sup>3</sup>Department of Orthopaedic Surgery, School of Medicine, Keio University, <sup>4</sup>Hamawaki Orthopaedic Hospital, <sup>5</sup>Osaka Police Hospital

Conflict of interest: None

[Background] Glycosylation is an important post-translational modification of proteins, influencing the biological functions and stability of the proteins. In Rheumatoid arthritis (RA) patients, autoantibodies frequently appear against IgG lacking galactose. Therefore, we hypothesized that abnormal glycosylation process are pathologically involved in RA.

Specifically, we focus on bone marrow (BM) as a causal lesion of RA. [Objective] To analyze the expression of glycosylation-related genes and their network regulation influencing immune regulation and inflammatory response. [Methods] Using DNA microarray data from the BM cells of 28 RA patients and 11 healthy individuals (HI), differentially expressed genes in RA were extracted compared to HI. Network analysis was also conducted. [Results] In RA, expression levels of glycosylation related genes such as A4GALT, UGCG, EXT and FUT8, significantly decreased. Meanwhile, expression levels of lectin genes such as ITGAL and SIGLEC increased. Both molecules bind to carbohydrate chains and interact with the inflammatory cytokines. They also compose a network relevant to a dendritic cells and NK cells functions. [Conclusion] In RA patient BM, expression levels of the glycosylation decreased while those of lectin genes significantly increased.

## P2-037

### Enhanced expression of mRNA for peptidylarginine deiminase 2 in CD34+ cells of the bone marrow in rheumatoid arthritis

Tatsuo Nagai<sup>1</sup>, Tetsuya Tomita<sup>2</sup>, Hideki Yoshikawa<sup>2</sup>, Shunsei Hirohata<sup>1</sup>  
<sup>1</sup>Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, <sup>2</sup>Department of Orthopaedic Surgery, Osaka University Graduate School of Medicine

Conflict of interest: None

[Objectives] Antibodies directed to citrullinated proteins are extremely specific for rheumatoid arthritis (RA). Citrullination is catalyzed by a group of peptidylarginine deiminase (PAD) enzymes. Several studies have disclosed that PAD2 and PAD4 are expressed in rheumatoid synovial tissue or in mononuclear cells of rheumatoid synovial fluid. The current study therefore examined the mRNA expression of PAD2 in bone marrow (BM) CD34+ cells from RA patients. [Methods] CD34+ cells were purified from BM samples from 48 RA patients and 30 OA patients during joint operations via aspiration from iliac crest. The expression of mRNA for PAD2 was examined by quantitative RT-PCR. [Results] The expression of mRNA for PAD2 was significantly higher in RA BM CD34+ cells than OA BM CD34+ cells. The PAD2 mRNA expression level was not correlated with the administration of MTX or oral steroid. PAD2 mRNA expression was significantly correlated with PAD4 and Sp1 transcription factor mRNA expression in RA BM CD34+ cells. [Conclusion] These results indicate that the enhanced expression of PAD2 mRNA in BM CD34+ cells plays a pivotal role in the pathogenesis of RA, and might be closely associated with the enhanced mRNA expression of PAD4 or Sp1.

## P2-038

### Correlation between Anti-cyclic Citrullinated Peptide Antibody Level and HB antibodies positivity in Patients with Rheumatoid Arthritis

Masao Sato<sup>1</sup>, Masao Takemura<sup>2</sup>

<sup>1</sup>Department of Rheumatology, Matsunami General Hospital, Gifu, Japan, <sup>2</sup>Department of Informative Laboratory Medicine, Gifu University Graduate School of Medicine

Conflict of interest: None

[Objectives] In this study, we analyzed whether anti-CCP antibody level and various background factors of RA patients, including the HB antibody positivity rate, are correlated. [Methods] As of March 2014, we successfully analyzed the anti-CCP antibody positivity rate and the correlation between HB antibodies (HBs and HBc) and various background factors of RA patients (age, onset time, disease duration, and drugs used) in 613 patients with ongoing RA treatment. [Results] The RA cases consisted of 138 male and 475 female patients (77.5%) aged 23–91 years (mean  $\pm$  SD, 63.1  $\pm$  13.3 years). Among the 613 cases, 398 (64.9%) were positive for anti-CCP antibody. The HBs antibody positive rates were 17.8% and 10.7% in the patients with positive and negative anti-CCP antibody results, respectively, indicating a significantly higher rate in the positive cases ( $p < 0.02$ ). The HBc antibody positive rates were 16.8% and 13.5%, respectively. No statistically significant difference but a higher trend was observed ( $p = 0.27$ ). [Conclusion] It is important to pay attention to the possible reactivation of HB when administering a strong immunosuppressive therapy to those with high HBs antibody positivity

rates and positive anti-CCP antibody results.

## P2-039

### Clinical characteristics of elderly-onset rheumatoid arthritis(EORA) with polymyalgia rheumatic(PMR)

Hironobu Nobata, Shogo Banno, Tomomichi Kasagi, Shie Ichihara, Miyoko Kunou, Hirokazu Imai  
Department of Internal Medicine, Division of Nephrology and Rheumatology, Aichi Medical University School of Medicine, Aichi, Japan

Conflict of interest: None

[Objectives] To clarify clinical features and therapeutic situation of EORA patients with accompanying PMR signs, we retrospectively analyzed 114 EORA patients, especially occurred over 65 years old. [Methods] Among 114 patients, we compared with 2 groups; 37 patients of PMR/RS3PE (EORA with PMR group), and 77 without these symptom (pure EORA group). Sixty-one pulmonary disease, 20 diabetic mellitus and 26 chronic kidney disease were recognized as underlying disorders. [Results] We compared laboratory findings and therapeutic situations between pure EORA group and EORA with PMR group as follows, respectively: RF (88.3%, 48.6%,  $p < 0.01$ ), ACPA (70.1%, 37.8%,  $p < 0.01$ ), PSL use (70.1%, 86.4%), mean initiation of PSL from diagnosis (1.09y, 0.33y,  $p = 0.056$ ), MTX use (75.3%, 86.5%), initiated MTX (1.46y, 0.58y,  $p = 0.025$ ), biologics use (50.0%, 24.3%,  $p < 0.01$ ), initiated biologics (3.49y, 1.70y,  $p = 0.118$ ). Abatacept was most frequently used. Eight cases complicated infection. [Conclusion] PSL and MTX were administered more early in EORA with PMR group. EORA with PMR patients were treated in early stage, and they achieve good therapeutic response. EORA patients treated biologics were not observed increased therapy related complications.

## P2-040

### Clinical features of seronegative elderly-onset rheumatoid arthritis

Keiichi Iwanami  
Nerima Hikarigaoka Hospital, Japan Association for Development of Community Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] To clarify the clinical features of seronegative elderly-onset rheumatoid arthritis. [Methods] The patients of Elderly-onset rheumatoid arthritis (EORA) who were diagnosed in our hospital were divided into two groups; the seropositive group (rheumatoid factor (RF) or anti-CCP antibodies (ACPA) positive) and the seronegative group (RF and ACPA negative). [Results] The number of patients and the average age in each group (SP vs SN) were 19 patients, 73.7 years, and 9 patients, 74.7 years, respectively. The sex ratio was 14:5 (female/male), and 5:4, respectively (not significant). At the time of diagnosis, the average mHAQ, CDAI and SDAI in each group were 0.31 vs 1.39 ( $p < 0.005$ ), 14.7 vs 26.4 ( $p < 0.005$ ), and 15.6 vs 35.7 and ( $p < 0.001$ ), respectively. Fever was frequently detected in the SN group (1/19 vs 7/9,  $p < 0.0005$ ). For the treatment, the administrations of PSL, MTX and biologics DMARDs were 1/19 vs 8/9 ( $p < 0.005$ ), 16/19 vs 8/9 (not significant) and 2/19 vs 5/9 ( $p < 0.05$ ), respectively. The SN group frequently required hospital admission (1/19 vs 4/9,  $p < 0.05$ ). The RA classification criteria of ACR / EULAR (2010) was less frequently met in the SN groups (19/19 vs 4/9,  $P < 0.005$ ). [Conclusion] Seronegative EORA is considered to be a subtype of RA or another disease entity.

## P2-041

### The transition of the subsets of joint destruction in the era in which the symptoms appear in the patients with rheumatoid arthritis

Norikazu Murata, Masao Yukioka  
Yukioka Hospital, Osaka, Japan

Conflict of interest: None

[Objectives] Verification of clinical impression that joint destruction has been receded recently with simple XP. [Methods] We differentiate the 291 female patients with rheumatoid arthritis (RA) whose disease du-

rations is over 10 years to 3 groups (MUD subset, MES subset and LES subset) by Ochi's method. Furthermore we investigate the relation of ACPA titers with joint destruction. [Results] The patients of onset in 1970s are divided into MUD48%, MES45% and LES7%. One in 1980s are 42%, 33%, 25%; one in 1990s are 13%, 36%, 51%; one in 2000s are 4%, 28%, 68%, respectively. Joint destruction is ameliorated remarkably in the patients of onset in 1990s and that inclination is more obvious in the group of onset in 2000s. ACPA (-) group is divided into MUD3.1%, MES21.9%, LES75.0%, ACPA low titer (<100) group is divided 22.5%, 35.1% and 42.3%, ACPA high titer (100<=) group is divided 28.0%, 37.3%, 34.7%, respectively. [Conclusion] Joint destruction is ameliorated remarkably in the patients of onset in 1990s (conventional DMARDs group) and that inclination is more obvious in the group of onset in 2000s (MTX and Biologics group).

## P2-042

### Assessment of the early good response to biological agents (biologics) as a clinical predictor in Rheumatoid arthritis (RA)

Shoko Tateishi<sup>1,2</sup>, Hiroko Kanda<sup>1,2</sup>, Harumi Shirai<sup>2</sup>, Yasuo Nagabuchi<sup>2</sup>, Kazuyoshi Ishigaki<sup>2</sup>, Yu Seri<sup>2</sup>, Toshiki Eri<sup>2</sup>, Lisa Akahira<sup>2</sup>, Miho Oshima<sup>2</sup>, Yumi Yamaguchi<sup>2</sup>, Yuta Kochi<sup>2</sup>, Eri Kinoshita<sup>2</sup>, Satoshi Shinohara<sup>2,3</sup>, Oh Sasaki<sup>2</sup>, Yukiko Iwasaki<sup>2</sup>, Hiroaki Harada<sup>2</sup>, Mihoko Shibuya<sup>2</sup>, Shuji Sumitomo<sup>2</sup>, Hirofumi Shoda<sup>2</sup>, Kanae Kubo<sup>2</sup>, Fujio Takeuchi<sup>2</sup>, Keishi Fujio<sup>2</sup>, Kazuhiko Yamamoto<sup>2</sup>

<sup>1</sup>Department of Immunotherapy Management, Graduate School of Medicine, University of Tokyo, Tokyo, Japan, <sup>2</sup>Department of Allergy and Rheumatology, The University of Tokyo, Tokyo, Japan, <sup>3</sup>Tochigi Rheumatic Clinic

Conflict of interest: Yes

[Objectives] We investigated whether the early good response to biologics can be used as a clinical predictor in RA. [Methods] Enrolled 50 patients with RA were started biologics and followed in our hospital for at least one year. Based on the EULAR response criteria, the differences in DASCRP between before and one month after starting biologics ( $\Delta$ DASCRP) were divided into good, moderate and no response group. At 6 months (mo.) and 12 mo., DAS28 values were collected and rates of low disease activity (LDA) were examined. [Results] Good response group achieved in remission of DASCRP at 6-mo. and the rate of LDA in this group was 73% at 6-mo. and 78% at 12-mo. On the other hand, no response was 18% and 36%. In a sub-analysis by their age (65>: young vs.  $\geq$ 65: elderly), there was no significant difference at the rate of LDA in any group in elderly. In a sub-analysis of the type of the biologics (TNF vs. TCZ vs. ABT), good response of TNF and TCZ were in remission at 12-mo. But this group of ABT had moderate disease activity in the mean of DASCRP. [Conclusion] Good response in  $\Delta$ DASCRP at one month after biologics might be the predictor of the achievement of LDA at 12 months in young RA with TNF or TCZ.

## P2-043

### Effectiveness of early treatment for elderly onset Rheumatoid Arthritis

Takuji Nishikawa<sup>1</sup>, Hiroshi Takahashi<sup>1</sup>, Kenichi Shimane<sup>1</sup>, Yuichi Nagase<sup>1</sup>, Gen Momoyama<sup>2</sup>, Shoichi Nagashima<sup>3</sup>

<sup>1</sup>Department of Rheumatology, Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan, <sup>2</sup>Department of Rheumatology, Tokyo Metropolitan Tama General Hospital, Tokyo, Japan, <sup>3</sup>Department of Orthopaedic Surgery, Heisei Tateishi Hospital, Tokyo, Japan

Conflict of interest: None

[Objectives] We aimed to evaluate early treatment for elderly onset Rheumatoid Arthritis (EORA) in comparison to that for young onset Rheumatoid Arthritis (YORA). [Methods] Fifty-five early onset Rheumatoid Arthritis patients was divided to twenty-three EORA patients and thirty-two YORA patients. We compared drugs for treatment and disease activities between these two groups at the time of initial treatment and after a year. [Results] MTX was used at the rate of 47.8% in EORA group and 40.6% in YORA group at the time of initial treatment and 90.9%, 100% after a year, respectively. The median dose of MTX was from 5.1 to 7.1 mg /week in EORA group and from 5.5 to 8.6mg /week in YORA

group. Sulfasalazine was used in seven cases at first and eight cases after a year in EORA and eleven cases, eight cases, respectively in YORA. Bucillamine was used in five cases at first and six cases after a year in EORA and five cases, both in YORA. Biologic agents was not used at first in both groups and two and six cases, respectively after a year. Disease remission was achieved at the rate of 69.6% in EORA group and 59.4% in YORA group. The rate of DAS28 no response was 8.7%, 15.6%, respectively. [Conclusion] Early treatment for EORA was also very effective compared to that for YORA.

## P2-044

### Discrepancy between CRP and ESR in patients with rheumatoid arthritis

Yuko Kaneko, Tsutomu Takeuchi

Division of Rheumatology, Department of Internal Medicine, Keio University

Conflict of interest: Yes

[Objectives] To identify factors that causes the discrepancy between CRP and ESR in patients with rheumatoid arthritis. [Methods] Patients with rheumatoid arthritis (RA) who visited to Keio University Hospital regularly were enrolled in this study. The results of CRP and ESR were obtained cross-sectionally. We divided patients according to values of CRP and ESR and compared them in background features, disease activity, and treatment. [Results] 1,402 patients were included. 560 (36.3%) patients showed both normal CRP and ESR. 329 (23.5%) had elevated CRP and 866 (61.8%) elevated ESR. When we compared 26 patients with elevated CRP and normal ESR and 563 with normal CRP and elevated ESR, the CRP elevated group was younger (55 vs 62 yo,  $P=0.006$ ), had more swollen joints (2.5 vs 1.2,  $P=0.01$ ), and got the worse evaluators' visual analog scale (VAS). There was no difference in patient general VAS, pain VAS, and HAQ. The proportion of patients treated with biologic agents was not significantly different, but the duration of biologic agent use was shorter in patients with elevated CRP and normal ESR. [Conclusion] The factors that cause the discrepancy between CRP and ESR were identified.

## P2-045

### MRI osteitis at baseline predicts the development of rapid radiographic progression at 1 year toward patients with early-stage rheumatoid arthritis: Results from Nagasaki University Early Arthritis Cohort

Yoshikazu Nakashima<sup>1</sup>, Mami Tamai<sup>1</sup>, Junko Kita<sup>1</sup>, Shoichi Fukui<sup>1</sup>, Masataka Umeda<sup>1</sup>, Ayako Nishino<sup>1</sup>, Takahisa Suzuki<sup>1</sup>, Yoshiro Horai<sup>1</sup>, Akitomo Okada<sup>2</sup>, Tomohiro Koga<sup>1</sup>, Shin-ya Kawashiri<sup>3,1</sup>, Naoki Iwamoto<sup>1</sup>, Kunihiro Ichinose<sup>1</sup>, Yasuko Hirai<sup>1</sup>, Kazuhiko Arima<sup>3</sup>, Hideki Nakamura<sup>1</sup>, Tomoki Origuchi<sup>4</sup>, Masataka Uetani<sup>5</sup>, Kiyoshi Aoyagi<sup>3</sup>, Katsumi Eguchi<sup>6</sup>, Atsushi Kawakami<sup>1</sup>

<sup>1</sup>Department of Immunology and Rheumatology, Nagasaki University Hospital, <sup>2</sup>Japanese Red Cross Nagasaki Genbaku Hospital, <sup>3</sup>Department of Public Health, Nagasaki University, <sup>4</sup>Nagasaki University Graduate School of Biomedical Sciences, <sup>5</sup>Department of Radiology, Nagasaki University Hospital, <sup>6</sup>Sasebo City General Hospital

Conflict of interest: None

[Objectives] We have tried to examine whether MRI osteitis predict the further development of RRP in patients with early-stage RA from Nagasaki University Early Arthritis Cohort. [Methods] This is a 1-year observational study from seventy-six patients in which the subjects received Gd-enhanced MRI of both wrists and finger joints. Synovitis, osteitis and bone erosion determined was scored by RAMRIS. Plain radiographic outcome was scored by Genant-modified Sharp score and RRP at 1 year in this study was identified as a score > 3 units/year. The clinical response toward introduction of DMARDs at 3 months was defined according to DAS28-EULAR response criteria. [Results] Median age and disease duration at entry were 54.5 y.o and 3 months, respectively. RRP was developed in 12 patients at 1 year. Multivariate logistic regression analysis have identified that RAMRIS osteitis score at baseline (1 increase, Odds ratio: 1.12, 95% C.I.: 1.06-1.19,  $p = 0.0002$ ) is the only independent predictor toward the development of RRP at 1 year. [Conclusion] Present

data suggest that MRI osteitis is closely associated with poor radiographic outcome in patients with early-stage RA. Physicians should especially consider the tight control of disease activity if MRI osteitis is obvious in early RA patients.

## P2-046

### In patients with female articular rheumatism introduced biological preparation into newly, can the serum MMP-3 level guess from disease activity?

Hidekazu Furuya, Ryo Yanai, Mayu Saito, Sakiko Isojima, Yusuke Miwa, Tsuyoshi Kasama

Division of Rheumatology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] serum MMP-3 value in the evaluation of synovitis in rheumatoid arthritis patients have been useful. Was examined the relationship between disease activity and serum MMP-3 value using the data of RA patients by introducing biologics newly. [Methods] in 2008-2014, female RA patients who have been introduced biologics at our hospital, after the start of treatment 14 weeks 3 and 30 weeks and I have examined the relationship of serum MMP-3 and disease activity of RA (SDAI, CDAI). In addition, those that are using steroids were excluded. Method of analysis are Spearman's rank correlation coefficient and logistic regression analysis. [Results] 73 people (IFN22, ETN6, TCZ15, ADA14, ABT6, GLM3, CZP7) were included, median age is 59 (26-78) years. After 14 weeks and 30 weeks MMP-3 value SDAI (14 weeks:  $r_s = 0.40$ ,  $p < 0.05$  30 weeks:  $r_s = 0.39$ ,  $p < 0.05$ ), CDAI (14 weeks:  $r_s = 0.37$ ,  $p < 0.05$  30 weeks:  $r_s = 0.35$ ,  $p < 0.05$ ) with a significant correlation. Calculates the ROC curve, was determined the cutoff value of MMP-3 values in remission criteria SDAI: 58ng / ml (14 weeks), 37.4ng / ml (30 weeks), CDAI: 56.3ng / ml (14), it was 37.4ng / ml (30). [Conclusion] Serum MMP-3 value in the evaluation of disease activity assessment and remissions female RA patients is useful.

## P2-047

### Efficacy of ultrasound examination only for clinically-determined involved joints when assessing secession of biologics in rheumatoid arthritis patients

Yusuke Yamada, Michihiro Ogasawara, Misa Gorai, Yuko Matsuki, Go Murayama, Nagachika Sugisaki, Takuya Nemoto, Seiichiro Ando, Kentaro Minowa, Takayuki Kon, Kurisu Tada, Masakazu Matsushita, Kazuhisa Nozawa, Ken Yamaji, Naoto Tamura, Yoshinari Takasaki  
Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] To investigate the utility of ultrasound (US) when assessing secession of biologics in RA patients with clinical remission. [Methods] When biologics were ceased by attending, US, SDAI, and HAQ were examined at baseline, every 3 months to one year. US was performed only for joints that clinically or objectively determined involved joints. Of enrolled 22 patients, 11 patients after 12 months' follow-up period were analyzed here. [Results] 8/11 patients could discontinue biologics for 12 months. Of then, 5/8 did not show US synovitis reappearance, 3/8 showed US synovitis reappearance without need for re-starting biologics. 3/11 needed to restart IFX, of then, 2/3 showed moderate residual US synovitis at the baseline assessment. [Conclusion] US synovitis reappearance was observed still in the case of no US synovitis at the baseline. Regular US examination gave us the chances to assess early therapy intensification. When moderate synovitis were observed in 2 joints or more, US synovitis reappearance were observed at early point. It might be one condition that we should abandon secession of biologics. No residual US synovitis could be necessary condition for biological discontinuation and we need further analysis by comparing US findings with other clinical information.

## P2-048

### Evaluation of musculoskeletal ultrasonography and biomarkers in RA patients treated with MTX

Takahisa Suzuki<sup>1</sup>, Naoki Iwamoto<sup>1</sup>, Ayako Nishino<sup>1</sup>, Shin-ya Kawashiri<sup>1,2</sup>, Akitomo Okada<sup>3</sup>, Toshiyuki Aramaki<sup>4</sup>, Yoshikazu Nakashima<sup>1</sup>, Yoshiro Horai<sup>1</sup>, Kunihiro Ichinose<sup>1</sup>, Kazuhiko Arima<sup>2</sup>, Mami Tamai<sup>1</sup>, Hideki Nakamura<sup>1</sup>, Tomoki Origuchi<sup>1,5</sup>, Atsushi Kawakami<sup>1</sup>

<sup>1</sup>Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, <sup>2</sup>Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, <sup>3</sup>The Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan, <sup>4</sup>Sasebo Chuo Hospital, Sasebo, Japan, <sup>5</sup>Department of Health Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Conflict of interest: None

[Objectives] To evaluate the efficacy of US assessment in patients with active rheumatoid arthritis (RA) through methotrexate (MTX) therapy. We also aimed to demonstrate the correlation between US assessment and biomarkers. [Methods] 35 active RA patients who had newly received methotrexate treatment were enrolled. Patients examined clinical, laboratory, and ultrasonography (US) evaluation at baseline, 3 months, and 6 months. Van der Heijde modified total Sharp score (TSS) and biomarkers, such as interleukin 6 (IL-6), vascular endothelial growth factor (VEGF) and tumor necrosis factor alpha (TNF- $\alpha$ ), were evaluated at baseline and 6months. [Results] GS score, PD score and DAS28-ESR were significantly decreased after six months MTX therapy. Furthermore, changes in DAS28-ESR were clearly associated with those in GS score and PD score. Among biomarker investigation, changes of IL-6 was significantly correlated with change of US assessment and DAS28-ESR. [Conclusion] US assessment was useful to evaluate the efficacy of MTX treatment from the early period, and US findings at 3months might predict disease activity at 6months. Additionally, IL-6 might be a useful biomarker in RA patients treated with MTX.

## P2-049

### Clinical, structural and functional evaluation in rheumatoid arthritis patients diagnosed after release of biologic-DMARDs

Michitomo Sakuma<sup>1</sup>, Kensuke Koyama<sup>2</sup>, Kozo Chino<sup>1</sup>, Hiroaki Iwase<sup>1</sup>, Yoshihiro Taykayama<sup>1</sup>, Hirotaka Haro<sup>2</sup>

<sup>1</sup>Dept. of Orthopaedic Surgery, Yamanashi Prefectural Central Hospital, <sup>2</sup>Dept. of Orthopaedic Surgery, University of Yamanashi

Conflict of interest: None

[Objectives] clinical remission is the important goal in rheumatoid arthritis (RA) We analyzed clinical, structural and functional evaluation in rheumatoid arthritis patients diagnosed between 2003 and October, 2014 after release of biologic-DMARDs [Methods] The study included 53patients (12 males and 41 females, the mean age 60 years (26-83), the mean disease duration was 6.3 years (1-11). Clinical, structural and functional evaluation was evaluated and examined using disease activity DAS28-ESR, Larsen grade of the wrist joint and mHAQ. [Results] Rate of patients with MTX: 84.9% (8.84mg/week), biologic DMARDs: 26.4%, glucocorticoid therapy: 37.7% (4.2mg/day). 6 patients, 8joints treated with joint surgery: total knee arthroplasty; 4, total hip arthroplasty; 3, ankledehis; 1. DAS28-ESR were achieved remission: 25, low activity: 14, moderate activity: 12, high activity: 2 patients, Larsen grade of the wrist joint, grade 0: 15. I: 17, II: 7, III: 9, IV: 4, V: 1.52 cases were achieved mHAQ remission (<0.5). [Conclusion] Many cases were achieved clinical and functional remission, but joint destruction of the wrist was progressing according to the disease duration. Conflict of interest: None

## P2-050

### Comparison of awareness between rheumatologist's rheumatoid arthritis patients (Specialist RA) and general doctor's rheumatoid arthritis patients (general RA) – Is is T2T practice different?

Keiko Funahashi<sup>1</sup>, Tsukasa Matsubara<sup>2</sup>, Akira Sagawa<sup>3</sup>, Hiroaki Matsuno<sup>3</sup>, Tomomaro Izumihara<sup>3</sup>

<sup>1</sup>Clinical Research, Matsubara Mayflower Hospital, Hyogo, Japan,

<sup>2</sup>Rheumatology, Matsubara Mayflower Hospital, Hyogo, Japan, <sup>3</sup>Japanese Clinician's Biologic Research Group, Hyogo, Japan

Conflict of interest: Yes

[Objectives] The last RA patient's survey showed a difference in outlook regarding T2T between RA patients treated by biological and conventional DMARDs patients, but not differences between RA specialists and general physicians. We surveyed RA public lecture attendants and analyzed differences between specialist RA (SRA) and general RA (GRA). [Methods] The JCBRG patient survey was used for SRA, and the survey given public lecture attendants 105 (2013) and 106 (2014) for GRA. We asked patient background, medication, satisfaction of treatment, coping with biological DMARDs, and expectations of doctors. [Results] Background did not differ, but the rate of "satisfaction of treatment" is 75% of SRA, but 35% of GRA. 35% of SRA are open to biological DMARDs vs. 20% of GRA, but 30% of GRA agree to treat with biological DMARDs if they can attain perfect remission, twice that of SRA. The rate of "No questions for attending doctor" was 40% of SRA, but 15% on GRA. GRA don't have clear goals of treatment and expectations of GRA was different from specialist RA. [Conclusion] This results indicated it was more important for RA education at facilities to achieve T2T. They also indicated there was not a marked difference in education level for RA between 2013 and 2014, and that we must educate GRA.

## P2-051

### Comparison with Clinical Results and Radiographic Joint Damage in Patients with Rheumatoid Arthritis with the Continuation or Discontinuation of Rapid3 Remission during 1 year

Kou Katayama<sup>1</sup>, Satomi Abe<sup>2</sup>, Tamotsu Kamishima<sup>3</sup>

<sup>1</sup>Katayama Orthopedic Rheumatology Clinic, <sup>2</sup>Department of Orthopedic Surgery, Asahikawa Medical University, <sup>3</sup>Faculty of Health Science, Hokkaido University

Conflict of interest: None

[Objectives] To compare clinical results and radiographic joint damage (RJD) in RA patients with or without continuation of RAPID3 remission during 1 year. [Methods] RJD were analyzed by using modified total sharp scoring method (mTSS) in hands and feet X-ray films of patients at baseline and 1 year later. [Results] 132 patients were available for this study from 285 RAPID3 remission RA patients (22.6%) in 1262 RA patients. Eighty-nine patients (67.4%) achieved the continuation of RAPID3 remission during 1 year. Forty-two patients (32.6%) failed to the continuation of RAPID3 remission during 1 year. There were significant differences in age, duration of RA, DAS28-ESR, tender joint counts, swollen joint counts between two groups. The RAPID3, DAS28-ESR and CDAI in the discontinuation group at 1 year significantly increased ( $p < 0.001$ ), although those in the continuation group did not increase. The  $\Delta$ mTSS/year was 0.17 in the continuation group, and 0.41 in the discontinuation group, although significant differences were not observed ( $P = 0.054$ ). [Conclusion] The improvement of DAS28 and CDAI in RA patients with continuation of RAPID3 remission during 1 year compared with those with discontinuation of RAPID3 remission. Slight trend was observed in  $\Delta$ mTSS/y between two groups ( $P = 0.054$ ).

## P2-052

### Results of Multi-center Rheumatoid Arthritis (RA) Patient Survey (I) Comparison of patients on DMARDs and biologics (BIO)

Tomomaro Izumihara<sup>1</sup>, Tsukasa Matsubara<sup>1,2</sup>, Keiko Funahashi<sup>2</sup>, Hiroaki Matsuno<sup>1</sup>, Akira Sagawa<sup>1</sup>, Masanori Adachi<sup>1</sup>, Mitsuhiro Iwahashi<sup>1</sup>, Tetsu Oyama<sup>1</sup>, Yuichi Nishioka<sup>1</sup>, Keisuke Hashimoto<sup>1</sup>, Motohiro Oribe<sup>1</sup>, Yuichi Takahashi<sup>1</sup>, Kensuke Kume<sup>1</sup>, Eisuke Shono<sup>1</sup>, Takaki Nojima<sup>1</sup>, Nobumasa Miyake<sup>1</sup>, Akihiko Nakamura<sup>1</sup>, Takefumi Kato<sup>1</sup>, Eiji Otsuka<sup>1</sup>, Shigehito Kiyokawa<sup>1</sup>, Koji Taneichi<sup>1</sup>, Takanori Azuma<sup>1</sup>, Toshiaki Miyamoto<sup>1</sup>, Michio Minami<sup>1</sup>, Tomomi Tsuru<sup>1</sup>, Munenori Mochizuki<sup>1</sup>, Yukio Sato<sup>1</sup>

<sup>1</sup>Japanese Clinician's Biologics Research Group, <sup>2</sup>Matsubara Mayflower Hospital

Conflict of interest: Yes

[Objectives] Comparison of patients on DMARDs and BIO showed

high patient goals. The situation at other facilities were not clear. A multi-center survey was done. [Methods] Consent and background was obtained from 9437 patients at 51 facilities. Questions included desired information, expectations, of medications, disappointments, anxiety, BIO experience, treatment goals, satisfaction and et. The results for the two groups BIO (BG: 3363) and DMARDs (DG: 4535) were analyzed separately [Results] For 'expectations of medications', 'reliable effects' was most common, with little gap between groups. However, with 'continuation of effects', there was a difference. 'Treatment disappointment' was nearly double in BG, but reasons differed. Responses of 'adverse effects' and 'effectiveness' regarding 'anxiety when changing medications' were the most common in BG and DG, but 'diminishing effects' was more frequent in BG, related to 'disappointment in drugs'. While 'treatment goals' related to recovery of ADL were the most frequent in both groups, BG responded 'stop joint destruction' 1.5 times more often. Several BG group responses showed this expectation. [Conclusion] Similar patient trends were seen, that treatment goals of BG are higher and that T2T levels are the same.

## P2-053

### The utility of 2010 ACR/EULAR RA classification criteria in daily clinical practice: A 3-year follow-up

Yuji Kishimoto<sup>1</sup>, Masako Hayashibara<sup>1</sup>, Kenta Moriwaki<sup>1</sup>, Hiroshi Hagino<sup>2</sup>

<sup>1</sup>Division of Orthopedic Surgery, Faculty of Medicine, Tottori University, Tottori, Japan, <sup>2</sup>School of Health Science, Faculty of Medicine, Tottori University, Tottori, Japan

Conflict of interest: None

[Objectives] To assess the utility of 2010 ACR/EULAR RA classification criteria in daily clinical practice with 3-year follow-up. [Methods] RA patients over a 3-year follow-up period were divided into two groups. Group A (n=19): RA patients fulfilling only 2010 criteria at diagnosis, and Group B (n=30): RA patients fulfilling both 2010 and 1987 criteria. Age, duration from onset to diagnosis, rheumatoid factor, ACPA at the time of diagnosis, and CRP, ESR, serum MMP-3, SDAI, mTSS, HAQ-DI at the time of diagnosis and 3 years after diagnosis were investigated and compared between 2 groups. In addition, remission and low disease activity rate, and the proportion of patients treated with MTX/bDMARDs at 3 years after diagnosis were also compared. [Results] At the time of diagnosis, CRP and SDAI were significantly low in group A. At 3 years after diagnosis, the proportion of patients treated with both MTX and bDMARDs were significantly low in group A, whereas other factors showed no significant differences. [Conclusion] The current study suggests that 2010 criteria facilitate early therapeutic intervention and may allow to accomplish clinical remission or low disease activity without administration of MTX/bDMARDs.

## P2-054

### The mid-term joint destruction predicted by the short-term clinical findings in patients with rheumatoid arthritis

Yuji Kishimoto<sup>1</sup>, Masako Hayashibara<sup>1</sup>, Kenta Moriwaki<sup>1</sup>, Hiroshi Hagino<sup>2</sup>

<sup>1</sup>Division of Orthopedic Surgery, Faculty of Medicine, Tottori University, Tottori, Japan, <sup>2</sup>School of Health Science, Faculty of Medicine, Tottori University, Tottori, Japan

Conflict of interest: None

[Objective] To evaluate the mid-term predictability of joint destruction based on the short-term clinical outcomes in RA patients. [Methods] Forty-eight RA patients who met the criteria; less than 1 year disease duration, without a treatment history of DMARDs, and over a consecutive 3 year follow-up, were enrolled and investigated mTSS at baseline and 3-4 years after diagnosis. Based on  $\Delta$ mTSS, patients were divided into 2 groups. Group A (n=8):  $\Delta$ mTSS  $\geq 3$ /year, Group B (n=40):  $\Delta$ mTSS  $< 3$ /year. Age, rheumatoid factor, ACPA, HAQ-DI, mTSS at diagnosis, and CRP, ESR, serum MMP-3, CDAI at the time of diagnosis, 3 month (3Mo) and 6 month (6Mo) after diagnosis were compared between 2 groups. Mann-Whitney U's test was used to compare, and the factors which showed  $p$ -value  $< 0.1$  were applied to logistic regression analysis. We considered the factors showed  $p < 0.05$  in logistic regression analysis as predictive factor. [Results] In univariate analysis, ESR, ACPA, mTSS, CDAI

at diagnosis, ESR, MMP-3 at 3 Mo, and CRP, ESR, MMP-3, CDAI at 6 Mo were significantly high in group A. In logistic regression analysis, CDAI at 6 Mo represented  $p$ -value=0.05 (odds ratio: 1.28, 95%CI: 1.00-1.64). [Discussion] The CDAI at 6 Mo may predict the mid-term joint destruction.

## P2-055

### Clinical remission rate of Rheumatoid Arthritis achieved by corticosteroids therapy was relatively less likely sustained; an analysis of National Database of Rheumatic Diseases in Japan

Takuma Koyama<sup>1</sup>, Jinju Nishino<sup>2,1</sup>, Naoko Shoda<sup>1</sup>, Yasunori Omata<sup>1</sup>, Tetsuro Yasui<sup>1</sup>, Yuho Kadono<sup>1</sup>, Toshihiro Matsui<sup>3</sup>, Sakae Tanaka<sup>1</sup>, Shigeto Tohma<sup>3</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, <sup>2</sup>Orthopaedic Surgeon, Nishino Clinic Orthopedics and Rheumatology, <sup>3</sup>Department of Rheumatology, Sagami National Hospital, National Hospital Organization (NHO)

Conflict of interest: None

**Objective:** The purpose of this study is to evaluate the sustainability of clinical remission of Rheumatoid Arthritis and to investigate which factors influence the results. **Materials & Methods:** Data collected from a national observational database of RA patients (National Database of Rheumatic Diseases by iR-net in Japan; NinJa) from 2011 to 2013 were analyzed for 374 RA patients. All patients had DAS28 < 2.6, achieving clinical remission in the year of 2011. We investigated how many patients had sustained clinical remission in 2013. We also analyzed whether the use of corticosteroids, Methotrexate, or biologic agents influenced the rate of future sustained remission. **Results:** Of 374 patients, 220 (58.8%) maintained clinical remission for two years. One hundred and fifty-five were administered corticosteroids and 216 were not. Eighty-one patients of steroid users (51.3%) and 154 without steroid use (64.4%) maintained remission for two years. The remission rate differed significantly depending on corticosteroids use. We did not find differences in the use of MTX or biologic agents. There was adjustment in the dose of corticosteroids or MTX. **Conclusions:** Clinical remission achieved by corticosteroids may have relative difficulty in sustainability.

## P2-056

### Anti-Major Histocompatibility Complex Class I-Related Chain A (MICA) Antibodies in Rheumatoid Arthritis Patients with Interstitial Lung Disease

Hiroshi Furukawa<sup>1</sup>, Shomi Oka<sup>1</sup>, Kota Shimada<sup>2</sup>, Akiko Komiya<sup>1</sup>, Naoyuki Tsuchiya<sup>3</sup>, Shigeto Tohma<sup>1</sup>

<sup>1</sup>Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami National Hospital, Sagami, Japan, <sup>2</sup>Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, Fuchu, Japan, <sup>3</sup>Molecular and Genetic Epidemiology Laboratory, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

Conflict of interest: Yes

**[Objectives]** Interstitial lung disease (ILD) is frequently associated with rheumatoid arthritis (RA), and is designated RA-associated ILD (RA-ILD) that influences the prognosis of the disease. Here, we investigated the anti-HLA antibody profiles to determine whether they may be useful for diagnosing RA-ILD. **[Methods]** Anti-HLA antibody levels were analyzed using the Lambda Array Beads Multi-Analyte System in 34 RA patients with or without RA-ILD. **[Results]** Average anti-major histocompatibility complex class I-related chain A (MICA) antibody levels were higher in RA patients with ILD than in those without ( $P=0.0013$ ). Average anti-HLA class I or class II antibody levels were not significantly different ( $P=0.6419$  and  $0.2486$ , respectively). The ratio of (average anti-MICA antibody levels)/(average anti-HLA class I antibody levels) was increased ( $P=4.47 \times 10^{-5}$ ). The area under the curve value of receiver operating characteristic curves of the ratio was 0.912. The optimized cut-off level of the ratio was determined for RA-ILD, and the specificity and the sensitivity were 88.2% and 82.4%, respectively. **[Conclusion]** To the best of our knowledge, this is the first report of anti-HLA antibody profiles in RA-ILD. The ratio of could be a better marker for diagnosing RA-ILD.

## P2-057

### Efficacy and safety of the treatment with biologic agents in rheumatoid arthritis patients with interstitial lung disease

Takahiro Kawasaki, Jun Fukui, Hachiro Konaka, Takayoshi Morita, Jun Fujimoto, Yasuhiro Kato, Yoshiyuki Mori, Kumiko Kobayashi, Hiroshi Fujiwara

Division of Rheumatology, Osaka General Medical Center, Osaka, Japan

Conflict of interest: None

**[Objectives]** To examine the efficacy and safety of biologics when they are administered to rheumatoid arthritis (RA) patients with interstitial lung disease (ILD). **[Methods]** We retrospectively assessed 18 RA patients who had been diagnosed with pre-existing ILD by computed tomography and were commenced on biologics in our division from April 2010 to December 2013. **[Results]** Out of 18 patients, 6 were male and 12 were female. The mean age was 70. Twenty seven biologics were administered to them. Out of them, 4 were infliximab (IFX), 6 were etanercept (ETN), 2 were golimumab (GLM), 7 were tocilizumab (TCZ), and 8 were abatacept (ABT). Efficacy of them was assessed the change of mean CDAI in six months after the administration with LOCF analysis. The changes in the each biologics were from 14.8 to 8.8 in IFX, from 27.4 to 13.3 in ETN, from 26.7 to 15.4 in GLM, from 29.5 to 12.4 in TCZ, from 19.4 to 18.3 in ABT, respectively. Of these, the improvement of CDAI was statistically significant in only TCZ ( $p=0.0028$ ). Exacerbations of ILD were occurred in 3 cases (11.1%), which were 2 ETN users and 1 GLM users. **[Conclusion]** Only TCZ significantly improved RA activity without exacerbation of ILD. It suggested that TCZ may be a useful therapeutic agent even in RA patients with ILD.

## P2-058

### Two years safety of abatacept therapy in Japanese patients with rheumatoid arthritis associated interstitial lung disease

Hirofumi Mitomi, Hidehiro Yamada, Yoshioki Yamasaki, Hiromi Matsushita, Machiko Mizushima, Hiroshi Ito, Teisuke Uchida, Seido Ooka, Hiroko Nagafuchi, Takahiro Okazaki, Shoichi Ozaki

Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna University School of Medicine, Kanagawa, Japan

Conflict of interest: None

**[Objectives]** Interstitial lung disease (ILD) is one of the important and occasionally fatal complications in rheumatoid arthritis (RA). We retrospectively investigated whether RA associated ILD (RA-ILD) could exacerbate upon abatacept (ABT) therapy. **[Methods]** We retrospectively reviewed the medical records of 17 Japanese patients complicated with RA-ILD who received by ABT. Pulmonary function test, serum KL-6 and chest HRCT were evaluated at 2 years after administration of ABT. **[Results]** 17 patients (64% were female) with RA-ILD were included this study. At the enrollment, the median age was 70 years, and the median disease duration (IQR) of RA was 96 (2-360) months. Significant deterioration of RA-ILD was not observed in terms of %VC (from  $90.6 \pm 19.2$  to  $83.4 \pm 18.6$  %) and KL-6 (from  $716 \pm 438$  to  $925 \pm 623$  IU/ml) after 2 years, and there were no patients who showed ILD exacerbation or respiratory tract infection. **[Conclusion]** ABT could be used safely in patients with RA-ILD. Further studies will be needed to establish proper guideline for the use of ABT in RA-ILD.

## P2-059

### Association of Human Leukocyte Antigen with Airway Diseases in Rheumatoid Arthritis

Shomi Oka<sup>1</sup>, Hiroshi Furukawa<sup>1</sup>, Kota Shimada<sup>2</sup>, Shoji Sugii<sup>2</sup>, Atsushi Hashimoto<sup>1</sup>, Akiko Komiya<sup>1</sup>, Akiko Suda<sup>3</sup>, Shinichiro Tsunoda<sup>4</sup>, Satoshi Ito<sup>5</sup>, Tadashi Nakamura<sup>6</sup>, Koichiro Saisho<sup>7</sup>, Hajime Sano<sup>4</sup>, Kiyoshi Migita<sup>8</sup>, Shohei Nagaoka<sup>3</sup>, Naoyuki Tsuchiya<sup>9</sup>, Shigeto Tohma<sup>1</sup>

<sup>1</sup>Sagami National Hospital, National Hospital Organization, Sagami, Japan, <sup>2</sup>Tokyo Metropolitan Tama Medical Center, Fuchu, Japan, <sup>3</sup>Yokohama Minami Kyosai Hospital, Yokohama, Japan, <sup>4</sup>Hyogo College of Medicine, Nishinomiya, Japan, <sup>5</sup>Niigata Rheumatic Center, Shibata, Japan, <sup>6</sup>Kumamoto Shinto General Hospital, Kumamoto, Japan, <sup>7</sup>Miyakonojo Hospital, National Hospital Organization, Miyakonojo, Japan, <sup>8</sup>Nagasaki Medical Center, National Hospital Organization, Omura, Japan, <sup>9</sup>Faculty



Conflict of interest: None

[Objectives] Interstitial lung disease (ILD) and airway diseases are frequently associated with rheumatoid arthritis (RA). Many studies for human leukocyte antigen (HLA) allelic association with RA have been reported, but a few have been validated in an RA subpopulation with ILD and AD. Associations of HLA alleles with ILD and airway diseases were investigated in this study. [Methods] An association study was conducted on *HLA-DRB1* and *DQB1* in Japanese RA patient with ILD, airway diseases, or emphysema, based on the findings of computed tomography images of the chest. [Results] DR2 serological group was associated with susceptibility to usual interstitial pneumonia ( $P=0.0036$ , odds ratio [OR] 1.86, 95% confidence interval [CI] 1.23-2.81). An association was found for shared epitope alleles with bronchiolitic airway disease ( $P=0.0040$ , OR 2.06, 95%CI 1.24-3.41). *DQB1\*03:01* was associated with bronchiectatic airway disease ( $P=0.0021$ ,  $P_c=0.0315$ , OR 1.99, 95%CI 1.30-3.06). *DQB1\*03:01* was also associated with emphysema ( $P=0.0007$ ,  $P_c=0.0104$ , OR 2.43, 95%CI 1.49-3.95). [Conclusion] This is the first identification of association of *HLA-DQB1\*03:01* with susceptibility to bronchiectatic airway disease or emphysema in RA.

## P2-060

### A case of rheumatoid arthritis whose interstitial lung disease exacerbated after cancer immunotherapy

Kotaro Matsumoto, Tamao Nakashita, Akira Jibatake, Akira Yoshida, Yuto Hamada, Shinji Motojima  
Kameda Medical Center, Rheumatology and Allergy, Kamogawa, Japan

Conflict of interest: None

The prognosis of pancreas cancer is very bad with 5 year survival rate of 5 %, and a lot of attentions have been paid not only on the development of new anti-cancer drugs but also cancer immunotherapy. Here we report a case of RA whose pre-existing interstitial lung disease (ILD) exacerbated after cancer immunotherapy. A 64 year-old woman was admitted to our hospital because of high blood glucose level on June 2014. She had been treated as a patient with RA with a combination of 2mg/day of PSL, 200mg/day of bucillamine, 1.5mg/day of tacrolimus, and twice a week of 25mg of etanercept. She had ILD, but it did not exacerbate during the treatment course. After admission, she had whole body examination, and a cancer of the pancreas head with liver metastasis was found. A biliary stent was inserted for obstructive jaundice, and cancer chemotherapy was done but was not effective. Because she strongly wanted to have cancer immunotherapy, she received 1 course of apoptosis-induction and cancer-peptide-induction therapy. One week after the cancer immunotherapy, pre-existing ILD began exacerbated, and 30mg/day of PSL started. ILD tended to improve, but cancer progressed rapidly resulting in death. We have to be careful for the exacerbation of ILD by cancer immunotherapy.

## P2-061

### A case of acute exacerbation of rheumatoid arthritis-associated interstitial lung disease in a patient on maintenance hemodialysis successfully treated with combination therapy of high-dose glucocorticoid, cyclophosphamide, and cyclosporine A

Takahiro Kawasaki, Jun Fukui, Hachiro Konaka, Jun Fujimoto, Kumiko Kobayashi, Hiroshi Fujiwara  
Division of Rheumatology, Osaka General Medical Center, Osaka, Japan

Conflict of interest: None

A 47-year-old woman who had been on maintenance hemodialysis (HD) due to IgA nephropathy was diagnosed with rheumatoid arthritis (RA) in April 2011. In July 2011, she acutely developed interstitial lung disease (ILD), and she was improved by high-dose glucocorticoid (GC). She had been stable with prednisolone (PSL) 10mg/day, but in January 2014, she was admitted to our hospital because of acute exacerbation of the ILD. At the time of admission, she was in acute respiratory failure with PaO<sub>2</sub> 69mmHg with oxygen supply of 2L/min, then the dose of PSL was increased to 60mg/day. However, ILD continued to deteriorate, so

intravenous methylprednisolone (MP) pulse therapy was started, and cyclosporine A (CyA) was added. Despite these treatments, the interstitial shadow exceedingly deteriorated and her respiratory condition got worse, so we repeated MP pulse therapy and also started intravenous cyclophosphamide therapy (IVCY). Then, ILD was gradually improved although she developed pneumomediastinum which disappeared during tapering of PSL. She was discharged on foot on 95 days after admission. We report this very rare case of acute exacerbation of RA-associated ILD in a patient on maintenance HD successfully treated with combination therapy of high-dose GC, IVCY, and CyA.

## P2-062

### Is there a discrepancy between estimated glomerular filtration rate; eGFR calculated by serum creatinin and eGFR calculated by cystatin C levels in patients with rheumatoid arthritis?

Junya Nagasawa, Ryosuke Hanaoka

Department of Rheumatology, Kamitsuga General Hospital, Tochigi, Japan

Conflict of interest: None

[Objectives] To determine whether there is a discrepancy between estimated glomerular filtration rate; eGFR calculated with serum creatinin and eGFR calculated with cystatin C levels in patients with rheumatoid arthritis. [Methods] We compared eGFR with serum creatinin levels (eGFR-Cr) and eGFR with serum cystatin C levels (eGFR-CysC) in the patients with RA. The difference of eGFR-Cr and eGFR-CysC is calculated and investigated associations with age, sex, height, weight, Body mass index (BMI), DAS28 ESR, disease duration of RA, and HAQ-DI. [Results] eGFR-Cr was significantly lower than eGFR-CysC ( $70.0 \pm 20.1$  vs.  $87.4 \pm 29.9$  ml/min/1.73m<sup>2</sup>,  $p=0.000$ ). The difference between eGFR-Cr and eGFR-CysC was correlated with height ( $p=0.004$ ), age ( $p=0.001$ ), disease duration ( $p=0.000$ ), DAS28 ESR ( $p=0.019$ ), and HAQ-DI ( $p=0.000$ ). Multiple linear regression analysis showed that higher age, longer disease duration, and high HAQ-DI independently correlated with the difference between eGFR-Cr and eGFR-CysC. [Conclusions] In the RA patient, eGFR-Cr may overestimate renal function disorder than eGFR-CysC. Longer disease duration, older age, and more serious disability may diminish the discrepancy between eGFR-Cr and eGFR-CysC.

## P2-063

### Sarcopenia in patients with rheumatoid arthritis is apparent, especially treated with biologics

Kentaro Inui<sup>1</sup>, Tatsuya Koike<sup>2,3</sup>, Masahiro Tada<sup>1</sup>, Yuko Sugioka<sup>1,2</sup>, Kenji Mamoto<sup>1</sup>, Tadashi Okano<sup>1</sup>, Hiroaki Nakamura<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Osaka City University Graduate School of Medicine, <sup>2</sup>Center for Senile Degenerative Disorders, Osaka City University Graduate School of Medicine, <sup>3</sup>Search Institute for Bone and Arthritis Disease, Shirahama Hamayu Hospital

Conflict of interest: None

**Objectives:** RA patients are at higher risk of metabolic syndrome and insulin resistance, therefore, sarcopenia related to metabolic syndrome is of concern. We conducted cross-sectional study to evaluate the relationship between skeletal muscle volume (ASMI), disease activity (DA) and insulin resistance. **Methods:** 202 RA patients and 202 age-, sex-matched healthy volunteers were enrolled. Laboratory data of lipid metabolism and insulin resistance were collected. ASMI was determined by whole body dual X-ray absorptiometry. **Results:** Sarcopenia was more apparent in RA patients than control ( $p<0.001$ ), especially in RA patients treated with biologics (BIO) (TNFi ( $p=0.004$ ); TCZ or ABT ( $p<0.001$ )). HOMA-R represented as insulin resistance was significantly higher in RA patients treated with TCZ or ABT than in control ( $p=0.019$ ). Regression correlation analysis among RA patients revealed strong and significant correlation between ASMI and BMI ( $R=0.553$ ;  $P<2.2e-16$ ), HOMA-R and BMI ( $R=0.304$ ;  $P=1.7e-5$ ). There was significant, but weak relationship between ASMI and DAS28 ( $R=-0.196$ ;  $P=0.0064$ ), ASMI and HOMA-R ( $R=0.145$ ;  $P=0.0447$ ). **Conclusion:** We showed that RA patients in higher DA, receiving BIO has less muscle volume. And insulin resistant was significantly lower in RA patients treated with BIO.

## P2-064

### Clinical and pathological characteristics of lymphoproliferative disorder in patients with rheumatoid arthritis

Hiroshi Fujinaga<sup>1</sup>, Tetsuo Watanabe<sup>1</sup>, Kozo Takahashi<sup>2</sup>, Toshiaki Kogure<sup>3</sup>  
<sup>1</sup>Department of Japanese Oriental Medicine and Rheumatology, Toyama Prefectural Central Hospital, Toyama, Japan, <sup>2</sup>Department of Clinical Laboratory, Toyama Prefectural Central Hospital, Toyama, Japan, <sup>3</sup>Department of Japanese Oriental Medicine, Gunma Central General Hospital, Maebashi, Japan

Conflict of interest: None

[Objectives] To investigate the clinical and pathological features of lymphoproliferative disorder (LPD) in patients (pts) with rheumatoid arthritis (RA). [Methods] Medical records of 18 RA pts who were diagnosed with LPD were retrospectively examined regarding clinical and pathological findings and treatment for RA. [Results] Of the 18 pts, 5 were male and 13 were female. The mean age at the onset of LPD was 70.3. Clinical features revealed that 6 pts had superficial lymph node swellings, 2 had abdominal lymph node swellings, 2 had pharyngeal ulcers, and 3 had lung tumors. Pathological findings revealed that 6 pts had DLBCL, 3 had FL, 2 had TCL, 1 had Burkitt lymphoma, 1 had HL, and 1 had Polymorphic/lymphoplasmacytic LPD. Nine pts improved only with the discontinuation of MTX. LPD was refractory in 8 pts, and they needed to undergo chemotherapy. After LPD onset, almost all pts were treated for RA with a small amount of prednisolone and DMARDs except for MTX, but 2 pts were retreated with a small amount of MTX. Tocilizumab and abatacept were used in 2 pts each. Six pts showed worsening RA disease activity after LPD onset. [Conclusion] After the withdrawal of MTX, immunosuppressants, and biologic DMARDs in pts with LPD, they frequently show the recurrence of RA disease activity.

## P2-065

### Efficacy and safety of iguratimod(IGU) in the patients of rheumatoid arthritis (RA) in our hospital

Takumi Matsumoto, Takao Katsuragawa, Hiroaki Tamura  
Department of Rheumatology, Kin-ikyō Chuo Hospital

Conflict of interest: None

[Objectives and Methods] To investigate efficacy and safety of IGU in all the patients of RA in our hospital, we researched on the reasons to administer IGU, trend of DAS28-CRP and SDAI, the reasons to stop IGU, and adverse events up to Oct. 31, 2014. [Results] We administered IGU to 24 cases (6 males). Age: 68.5±11.5 years old. Disease duration: 10.5±8.6 years. Six cases were stopped methotrexate because of malignant lymphoma (ML). Because of comorbidities except for ML, 9 cases had high risk of adverse events by other DMARDs. One case had tuberculosis of the lungs. One case Chronic hepatitis B. Main comorbidities: 3 cases had interstitial lung diseases, 6 cases had ML. When IGU was started, (DAS28-CRP, SDAI) = (3.8±1.0, 15.6±7.6, n=24), At the time of 4 weeks later: (3.3±1.1, 11.4±7.7, n=17), at 8 weeks: (2.8±1.2, 9.0±5.6, n=16), at 12 weeks: (3.0±1.1, 9.6±6.2, n=11), at 16 weeks: (3.0±1.6, 9.8±10.1, n=6), at 20 weeks: (2.7±1.2, 7.6±6.9, n=5), at 24 weeks: (2.4±0.7, 9.0±8.1, n=3). There were 5 adverse events such as liver dysfunction (2 cases), abdominal pain, numbness of lips, interaction between IGU and warfarin which administered by another clinic. [Conclusion] In most cases, IGU were administered to the patients at high risk because of their comorbidities. We confirmed improvements of DAS28-CRP and SDAI.

## P2-066

### The efficacy and safety of iguratimod in patients with rheumatoid arthritis at a single center

Keigo Setoguchi, Hou Chin, Satomi Kobayashi, Yasunobu Takizawa  
Department of Systemic Immunological Diseases, Tokyo Metropolitan Cancer and Infectious Diseases Komatome Hospital

Conflict of interest: None

[Objectives] To investigate the efficacy and safety of iguratimod in patients with rheumatoid arthritis (RA) who had inadequate response to

conventional therapy. [Methods] Ten men and 21 female patients with RA who visited Department of Systemic immunological diseases Tokyo Metropolitan Komagome Hospital between January 1, 2013 and April 30, 2014 were enrolled. Patients' age, clinical features, previous treatment were reviewed. Changes in DAS28-CRP at 6 months and 12 months were evaluated. [Results] Mean age at initiation of iguratimod was 69.8 years and mean disease duration was 10 years. Fifteen patients used MTX. Three patients had history of malignancy, two had interstitial pneumonia and one had chronic kidney disease in 16 patients who did not use MTX. Daily dose of iguratimod was 50mg in 18 patients and 25mg in 13 patients. The score of DAS28-CRP changed from 3.72±1.14 (N=28) at baseline to 3.06±1.04 (N=22) at 6 months and 2.93±1.09 (N=14) at 12 months. One patient ceased iguratimod for incidental finding of colon cancer. Other 8 patients including only one male patient ceased due to adverse events. [Conclusion] Iguratimod may be useful for male patients with moderate disease activity of RA.

## P2-067

### Efficacy of the clinical use of iguratimod in patients with rheumatoid arthritis

Atsunori Tokushige, Takashi Imagama, Kazushige Seki, Toshihiko Taguchi  
Department of Orthopedic Surgery, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan

Conflict of interest: None

[Objectives] The purpose of this study is to confirm the efficacy of iguratimod (IGU) for rheumatoid arthritis (RA) and predict of disease activity at 24 weeks from the patient's general health on visual analog scale (Pt VAS) at 4weeks. [Methods] Thirty-one patients enrolled in this study, and the improvement in RA was evaluated every 4weeks during the 24weeks. [Results] Twenty-three patients were added IGU to existing formula, eight patients were switched to IGU. Four patients were discontinued uses of IGU due to side effects and two patients were discontinued due to no effect. Twenty-two patients were Pt VAS, disease activity score (DAS) 28-CRP, CDAI, SDAI, mHAQ score were significantly decreased at week 24. The change rate of Pt VAS was calculated from Pt VAS before and 4weeks after used IGU ((before Pt VAS - 4weeks Pt VAS) / before Pt VAS)). The change rate of Pt VAS was significantly higher in remission and low disease activity group than moderate disease activity and no effect group. [Conclusion] IGU had significant clinical effects on the RA patients within 24 weeks. The change rate of Pt VAS before and 4weeks after used IGU have the potential to predict of disease activity at 24 weeks.

## P2-068

### Effects of iguratimod monotherapy in patients with rheumatoid arthritis

Yuichi Takahashi  
Yu Family Clinic

Conflict of interest: None

[Objective] To evaluate the effect of iguratimod (IGU) monotherapy in patients with rheumatoid arthritis (RA). [Methods] The subjects were 40 RA patients (34 women, 6 men). Iguratimod was administered at doses of 25 mg/day for the first 4 weeks and 50 mg/day thereafter. The effects of the drug were evaluated at Weeks 0, 12, 24, and 52 based on CRP levels and DAS28ESR scores. [Results] The mean CRP level and DAS28ESR score at Week 0 were 1.49±2.04 mg/dL and 4.35±1.12, respectively, indicating that the patients had moderate disease activity. The mean CRP levels at Weeks 12, 24, and 52 were 0.85±1.63, 0.83±1.28, and 0.44±0.51 mg/dL, respectively; and the mean DAS28ESR scores were 3.60±1.12, 3.74±1.18, and 3.38±1.18, respectively. Approximately 37%, 60%, and 50% of the patients showed low disease activity at Weeks 12, 24, and 52, respectively. In addition, approximately 39% of the patients satisfied the remission criteria at Week 52. [Conclusion] This study suggests that IGU monotherapy can contribute to the achievement of low disease activity and/or clinical remission in RA patients with moderate disease activity. Thus, IGU monotherapy is promising for the management of elderly RA patients and those unresponsive to methotrexate.

## P2-069

### Efficacy of early choice of methotrexate in elderly onset rheumatoid arthritis

Naofumi Chinen<sup>1</sup>, Takayuki Wakabayashi<sup>1</sup>, Yasuo Suzuki<sup>2</sup>

<sup>1</sup>Division of Rheumatology, Tokai University Hachioji Hospital, Tokyo, Japan, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Tokai University School of Medicine, Kanagawa, Japan

Conflict of interest: None

[Objectives] We investigate the efficacy of early choice of methotrexate (MTX), such as 1<sup>st</sup> or 2<sup>nd</sup> DMARDs, in elderly onset ( $\geq 65$  years old) rheumatoid arthritis (EORA). [Methods] Thirty three patient data with EORA were retrospectively collected from chart, divided into early MTX chosen group (1<sup>st</sup> or 2<sup>nd</sup> DMARD, n=14) and late MTX chosen group (3<sup>rd</sup> DMARD or later, n=19), and evaluated disease activity, course of treatments and newly onset complication. [Results] Patients data (early MTX chosen group vs late MTX chosen group) were onset  $70.4 \pm 0.8$  vs  $70.2 \pm 1.1$  years old, duration until treatment with MTX  $1.3 \pm 0.6$  vs  $2.1 \pm 0.6$  years. Prednisolone (PSL) use was lower at early group (36%, n=5 vs 79%, n=15). To compared with before and 2 years later from treatment with MTX, MTX dosage was higher in late group (from  $5.1 \pm 0.4$  vs  $5.3 \pm 0.4$  mg/week to  $6.0 \pm 1.0$  vs  $7.7 \pm 0.2$  mg/week), but improvement of DAS28 (ESR) was not difference (from  $5.43 \pm 0.71$  vs  $5.07 \pm 0.20$  to  $3.40 \pm 0.29$  vs  $3.39 \pm 0.24$ ). Throughout the course, MTX was continued long duration ( $7.3 \pm 1.0$  vs  $7.8 \pm 1.0$  years), and early group was lower PSL use (29%, n=4 vs 79%, n=15) and incidence of vertebral and femoral neck fracture (7%, n=1 vs 57%, n=8). [Conclusion] Early choice of MTX in EORA expect to decrease PSL use and complication of fracture.

## P2-070

### Persistence rate of methotrexate in treatment of rheumatoid arthritis

Tatsuo Hirose, Yuji Tasaka

Department of Internal Medicine, Saitama City Hospital

Conflict of interest: None

[Objectives] Methotrexate (MTX) is an important to the conventional care of patients with rheumatoid arthritis (RA). The aim of this study was to assess persistence with MTX and to identify reasons for drug discontinuation. [Methods] The patients with RA completed at least 5 years of follow-up were registered and persistence with MTX was examined. [Results] In total, 128 patients had completed at least 5 years of follow-up, 78.9% of whom remained on MTX. 47 patients had completed at least 10 years of follow-up, 66.0% of whom remained on MTX. During the period of follow-up, 16 cases discontinued within 4 weeks due to adverse events (vomiting, eruption, liver dysfunction or oral ulcer). 11 cases discontinued within 5 years (liver dysfunction 4, interstitial pneumonia 3). 8 cases discontinued within 10 years (pancytopenia 3, liver dysfunction 2). 3 cases of malignant lymphoma were detected during 2 to 7 years of follow-up. 3 cases were discontinued after 10 years due to contraindication by kidney dysfunction. 40 cases (31.2%) needed dose change of MTX, increased dose in 24 cases, and decreased dose in 16 cases. [Conclusion] RA patients show high persistence rates with MTX compared with other DMARDs, however some cases show serious adverse effects.

## P2-071

### Liver dysfunction in patients with rheumatoid arthritis treated by methotrexate

Masayuki Miyata

Department of Internal Medicine and Gastroenterology, Fukushima Red Cross Hospital, Fukushima, Japan

Conflict of interest: None

[Objectives] MTX is most important for the treatment of RA and called as anchor drug. The knock of the treatment of RA is how to use MTX effectively without side effect. The side effect such as liver dysfunction is seen frequently, which is recovered by the additional administration of folic acid. In some instances, recovery delays and continues. In that case, most of patients have non-alcoholic fatty liver: NAFL. [Methods] The patients with prolonged liver dysfunction were selected in 540

RA patients treated with MTX. Imaging examination such as US and CT scan as well as blood examination like hyaluronic acid and type IV collagen level measurement were performed. The patients who would have chronic hepatitis were selected and liver biopsy was performed. [Results] Four patients with non-alcoholic steatohepatitis: NASH were detected. Most had diabetes mellitus, dyslipidemia and obesity. [Conclusion] NAFL is easily diagnosed if the patients have diabetes mellitus, dyslipidemia and obesity. However, NASH can be found among those patients. We experienced one NASH patient without any risk for NAFL and we treated her with cease MTX. The mechanisms for NASH formation remains unclear in patients with RA treated with MTX. However, we have to be reminded that MTX accelerate fibrosis as side effect.

## P2-072

### Evaluation of the dosage change of methotrexate (MTX) after the approval of over-dose prescription of MTX and combinations of conventional DMARDs in our hospital

Yasuo Kuroki

Internal Medicine, Kobe century Memorial Hospital, Kobe, Japan

Conflict of interest: None

[Objective] To evaluate the change of MTX dosage and efficacy of combinations with conventional DMARDs. [Patients and Methods] 277 outpatients with RA treated with MTX and other disease-modifying antirheumatic drugs (DMARDs) in our hospital were investigated in this study. The change of the MTX dosage and the efficacy of combinations with other DMARDs are examined. The activity of RA was evaluated by CRP and DAS28-CRP score. [Results] Patients treated with MTX monotherapy were 175, and patients treated with over 10mg of MTX were 55 (31.4%), which was almost same with that reported in 2012. Thirty patients treated with MTX had combinations with other DMARDs, salazosulfapyridine (SASP) (n=10), bucillamine (Bc) (n=8), iguratimod (n=8), Tacrolimus (n=4), and three patients were treated with combinations of three DMARDs. Patients who could not take MTX because of adverse effects had combination therapy with SASP and Bc (n=10). Four of six patients with Leflunomide had monotherapy, and eight of 10 patients treated with iguratimod had combination with MTX. [Conclusion] The combination of conventional DMARDs seems to be effective, and it is necessary to establish algorithm of combination DMARDs therapy.

## P2-073

### Influence of the dosing schedule of methotrexate on antirheumatic effects in CIA rats

Hideto To

Department of Medical Pharmaceutics, Graduate School of Medicine and Pharmaceutical Sciences for Research University of Toyama, Toyama, Japan

Conflict of interest: None

[Objectives] We investigated the influence of the dosing schedule on antirheumatic effects following the administration of methotrexate (MTX) to CIA rats. [Methods] MTX was perorally administered, and CIA rats were divided into once-daily, once-weekly, and three times-weekly groups (12-hr intervals). [Results] No significant differences were observed in the arthritis scores of the control, once-weekly (7 mg/kg/time), and three times-weekly (2.33 mg/kg/time x 3) groups on day 22 when MTX had been administered to each group for 3 weeks one day after the first immunization. Arthritis was rarely observed in the once-daily (1 mg/kg/time x 7) group for the dosing period, and exacerbations in the arthritis score were inhibited more in the once-daily group than in the other dosing groups ( $P < 0.01$ , respectively). The arthritis score was also significantly lower in the once-daily (0.25 mg/kg/time x 7) group than in the three times-weekly (2.33 mg/kg/time x 3) group; however, the total dose in one week in the once-daily group was 25% that of the three times-weekly group ( $P < 0.01$ ). No group developed severe adverse effects. [Conclusion] These results demonstrated that the administration of MTX once a day was safer and improved RA symptoms more than current standard dosing methods.

## P2-074

### Tacrolimus in NinJa 2013 (Comparison of efficacy among treated with Tacrolimus mono-therapy and concomitant therapy with Tacrolimus)

Eisuke Ogawa<sup>1</sup>, Sumiaki Tanaka<sup>1</sup>, Yu Matsueda<sup>1</sup>, Nobuhiro Sho<sup>1</sup>, Yoshiyuki Arinuma<sup>1</sup>, Tatsuhiko Wada<sup>1</sup>, Tatsuo Nagai<sup>1</sup>, Shunsei Hirohata<sup>1</sup>, Toshihiro Matsui<sup>2</sup>, Shigeto Tohma<sup>3</sup>

<sup>1</sup>Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, <sup>2</sup>Department of Rheumatology, Sagami National Hospital, National Hospital Organization, <sup>3</sup>Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami National Hospital, Sagami, Japan

Conflict of interest: None

[Aim] To understand the use of Tacrolimus (TAC) in NinJa and their efficacy among TAC mono-therapy and concomitant therapy with TAC. [Methods] Using data of NinJa 2013, we selected RA patients treated with TAC and compared their disease activity and other data. The number of patients treated with TAC was 1373 included in treated with TAC-mono (441), biologics and tacrolimus (138), and tacrolimus and other single-species of DMARDs (715). Patients treated with ETN+TAC (48), TCZ+TAC (45) and ABT+TAC (36) were included in patients treated with TAC and biologics. And patients treated with MTX+TAC (399), SASP+TAC (100) and BUC+TAC (50) were included in patients treated with TAC and DMARDs. [Results] CDAI (mean±SD) was 7.70±7.77 in ETN+TAC, 11.5±9.42 in TCZ+TAC and 9.54±7.65 in ABT+TAC. CDAI was significantly lower in ETN+TAC than TCZ+TAC ( $p=0.0454$ ). DAS28-CRP (mean±SD) was 2.59±1.04 in MTX+TAC, 3.14±1.06 in SASP+TAC, 2.76±1.06 in BUC+TAC and 2.71±1.11 in TAC-mono. DAS28-CRP was significantly higher in SASP+TAC group than MTX+TAC group and TAC-mono group. Whereas, as for DAS28-CRP, there was no significant differences between BUC+TAC group, MTX+TAC group and TAC-mono group. [Conclusion] Our results demonstrate that CDAI was lower in ETN+TAC group. DAS28-CRP of BUC+TAC group was as good as MTX+TAC group.

## P2-075

### Methotrexate induced pancytopenia. Experience in my Clinic

Motohiro Oribe

Oribe Clinic of Rheumatism and Medicine

Conflict of interest: None

[Objective]: Low dose (6–16 mg/week) methotrexate is widely used for the management of systemic inflammatory diseases, and is considered to be relatively safe. I describe the experience and outcomes of low dose MTX toxicity in my private clinic. [Patients and methods]: We examined a retrospective case series of 8 patients (2 patients hospitalized at Oita Red Cross Hospital and 6 patients attempted pancytopenia) for low dose MTX toxicity. [Results]: Case 1 was 61 years male who had been dosing MTX 10mg/w with 82 months without folic acid resulted WBC counts 1700/mm<sup>3</sup>, hemoglobin (Hb) 6.1 g/dl and Platelet 8.4 x10<sup>4</sup> at hospitalization. Case 2 was 69 years female who had been dosing MTX 6mg/w with 52 months with folic acid resulted WBC counts 2000/mm<sup>3</sup>, Hb 6.9 g/dl and Platelet 2.4x10<sup>4</sup> at hospitalization. Those two cases rescued by Leucobolin in admission therapy. In another 6 cases who diagnosed by attempted pancytopenia showed, 4 cases were leucocytopenia, 5 cases were hypohemoglobinemia and 4 cases were thrombocytopenia respectively. [Conclusions]: Low-dose MTX toxicity can be life threatening, mainly due to myelosuppression. There is no rationale for MTX therapeutic drug monitoring in the setting of low-dose toxicity.

## P2-076

### Study of the efficacy of low-dose tacrolimus

Rie Kurose, Dai Tanaka, Yasuyuki Ishibashi

Department of Orthopaedic Surgery, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

Conflict of interest: None

[Objectives] In the treatment of RA, TAC is easy to use for cases in

which MTX cannot be used for complications and for cases in which the effect of MTX is poor. We investigated the efficacy of low-dose TAC. [Methods] Thirty-seven cases in which oral administration of TAC was possible more than 1 year between August 2006 and November 2013 in our hospital were estimated. [Results] Average dose of TAC was 1.16 mg/day at the first time and 1.28 mg/day at 1 year. In 25 cases, MTX of average dose of 7.46 mg/week was combined with TAC. In 18 cases, steroid of average dose of 4.89 mg/day was combined with TAC. A biologic agent was combined with TAC in one patient. DAS28-CRP was significantly improved at both 6 month and 1 year. Low disease activity and clinical remission were achieved in 8 and 5 cases, respectively. However, 9 cases did not show response by EULAR criteria. MMP-3 was significantly improved at both 6 month and 1 year. There was obvious correlation between DAS28-CRP and serum MMP-3. [Conclusions] Administration of low-dose TAC caused significant improvement both in the DAS28-CRP and serum MMP-3, while 24% of the patients showed no response.

## P2-077

### Treatment experience with elderly onset rheumatoid arthritis in our hospital

Katsuhiro Oi, Mitsuhiro Iwahashi, Jiro Yamana, Rie Sasaki, Seizo Yamana  
Higashi Hiroshima Memorial Hospital

Conflict of interest: None

[Object] We consider the optimal treatment for high disease activity and super-aged patients with rheumatoid arthritis. [Methods] Target cases were 13 people that was more than 80 years, showed CRP 5 or more, onset rheumatoid arthritis during 2010-2014, within one year of history to our hospital visits (average age 84.9 years). The treatment in our hospital were examined retrospectively, and evaluate the efficacy in DAS28-CRP. [Results] Type of drugs: Biological agents 2, Methotrexate 3, Bu-cillamine 5, Salazosulfapyridine 4, Tacrolimus 2, Mizoribine 1, Prednisolone 12, Prednisolone average 2.65mg. DAS28-CRP score had improved with the start of treatment after 1year average 1.97 ± 1.86 from pre-treatment average 3.96 ± 1.24. At time points after start of treatment one year, DAS28-CRP is under 2.3: 9 cases, from 2.3 to 2.7: 1 case, 2.7 to 4.1: 3 cases. [Conclusion] Utilization and retention rate of methotrexate was low for the elderly and mergers. Anti-CCP antibody-positive patients have a low remission, compared to the negative examples. To overall, small amount of steroids and immunomodulators had obtained a high remission rate, we considered that should be selected such treatment at first.

## P2-078

### Treatment for RA-related interstitial lung disease

Kazuhiro Otani, Tetsunao Matsushita, Koichi Nakagawa, Fumihisa Nakamura, Akihiro Moritake

Department of Orthopaedic Surgery, Kishiwada Municipal Hospital

Conflict of interest: None

[Objectives] There has been significant changes in the management of RA treatment. Strategy of treatment of RA shifts to use of DMARDs, such as MTX and biologic DMARDs. Approximately 10% of the patients with rheumatoid arthritis have clinically interstitial lung disease. DMARDs and biologic drugs may trigger or worsen RA-related interstitial lung disease (ILD). [Methods] Twenty one patients with RA-ILD of ninety eight RA patients were included in analysis. The subtype and extent of RA-ILD was examined by HRCT. PSL were administrated in 18 patients, MTX in 11, SASP in 8, TAC in 7, BUC in 3 and MZR in 3, respectively. Biologic drug was administrated in one case. [Results] KL-6 level was ranged from 228 to 1851 (average of 734) U/ml and ACPAs was ranged from 0.6 to 407 (average of 257) U/ml. In all patients, regular monitoring with comprehensive lung function and KL-6 level, initially at 3 months was performed by pulmonologists. No development of the lung disease was observed. [Conclusion] Treatment for RA with ILD involves corticosteroids, sometimes in conjunction with alternative immunosuppressive agents such as TAC and MZR. Under the support by radiologists and pulmonologists, we examined effective RA treatment with non-biologic or biologic DMARDs and monitored lung function.

## P2-079

### The effect and safety of additional administration of tacrolimus in rheumatoid arthritis patients with an inadequate response to tocilizumab

Shoichi Kaneshiro<sup>1</sup>, Kosuke Ebina<sup>2</sup>, Kenrin Shi<sup>2</sup>, Hideki Tsuboi<sup>3</sup>, Masataka Nishikawa<sup>1</sup>, Hajime Owaki<sup>1</sup>, Akihito Nampei<sup>4</sup>, Yoshio Nagayama<sup>4</sup>, Hideki Yoshikawa<sup>2</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Japan Community Health Care Organization, Osaka Hospital, <sup>2</sup>Department of Orthopaedic Surgery Osaka University Graduate School of Medicine, <sup>3</sup>Department of Rheumatology, National Hospital Organization Osaka Minami Medical Center, <sup>4</sup>Department of Orthopaedic Surgery, Osaka Rosai Hospital

Conflict of interest: None

**[Introduction]** Biologics for RA patients (Pts) are often discontinued due to inadequate response (IR) including primary and secondary ineffectiveness. There are few reports about hopeful add-on treatment options for RA Pts with IR to TCZ. In JCR 2014, we reported the effect and safety of additional administration of TAC in RA Pts with IR to TCZ. We report the new data including new cases. **[Pts and methods]** 18 RA Pts (mean age 58.6 yrs, disease duration 10.7 yrs, TCZ dosing duration 2.8 yrs) who had shown IR to TCZ were treated with TAC combination from 1/2012 until 10/2014. The effects and safety were evaluated at 8 weeks later. **[Results]** At the onset of TAC, 2 Pts showed high activity, 10 Pts moderate activity, 3 Pts low activity, and 3 Pts remission in RA disease activity. The scores of CDAI at the onset, and after 8 weeks were 16.6, and 9.1, respectively. The scores of DAS28-CRP were 3.15, and 2.36. The scores of MMP-3 were 229.3, and 85.5. They were significantly improved. 6 of 16 Pts achieved more than moderate response according to the EULAR improvement criteria. One Pt discontinued TAC due to IR, and one did due to adverse effects. No severe adverse effect was observed. **[Discussion]** TAC combination therapy may be useful for RA Pts that show IR to TCZ.

## P2-080

### Study for the patients with rheumatoid arthritis treated with long-term infliximab therapy: more than 50 infusions

Yasushi Miura<sup>1,2</sup>, Toshihisa Maeda<sup>2</sup>, Koji Fukuda<sup>3</sup>, Masahiro Kurosaka<sup>2</sup>  
<sup>1</sup>Dept. of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Japan, <sup>2</sup>Dept. of Orthopaedic Surgery, Kobe University Graduate School of Med., Kobe, Japan, <sup>3</sup>Dept. of Orthopaedic Surgery, Kakogawa City Hospital, Kakogawa, Japan

Conflict of interest: Yes

**[Objectives]** Eleven years have passed since infliximab (IFX) was approved for patients with rheumatoid arthritis (RA) in July 2003. In this study, we investigate the patients with RA treat with more than 50 infusions of IFX. **[Methods]** We retrospectively investigated the backgrounds and the current conditions of patients with RA treat with more than 50 infusions of IFX continuously. **[Results]** 17 patients (14 females, 3 males), age: 57.2 (31~82) y, disease duration: 19.7 (10~34) y, infusions of IFX: 60.6 (50~80) times, dose of IFX: 4.1 (2.5~6.8) mg/kg, intervals: 7.9 (6~9) w, dose of MTX: 8.5 (6~16) mg/w, combined usage of steroid (4 patients: PSL1~4mg/d), additional DMARDs usage (tacrolimus 5, leflunomide 2). Increase of IFX with the increase of vials: 4 (300mg: 1, 400mg: 1), without the increase of the vials: 8, 3mg/kg: 3, decrease: 2 patients. 8 patients achieved DAS28-ESR remission. Two patients were re-administrated IFX due to the exacerbation after bio-free remission was once achieved. **[Conclusion]** By the increase of dose and the shorten interval of IFX, additional usage of immune-suppressive agents, or increase of MTX dose, patients with RA may be treated well by IFX over a prolonged period.

## P2-081

### Efficacy of certolizumab pegol in our Department study

Toshiyuki Fujii

Osaka Saiseikai of Suita Orthopaedic, Osaka, Japan

Conflict of interest: None

**[Objectives]** To RA patient in whom MTX cannot be administered, RA treatment is difficult. This time, using certolizumab pegol (CZP) in RA patients in whom MTX cannot be administered, it is reported about its clinical efficacy. **[Methods]** In 8 patients with RA treated with CZP, MTX can be administered in 7 cases. All cases are women, average age is 66.9 years, Class classification average is 2.43, Stage classification average is 3.00, diseased period average is 11.4 years. 6 cases are naive, 1 example is switch from the Golimumab. CZP clinical performance (effectiveness) was evaluated in disease activity index (DAS28-ESR). **[Results and Conclusion]** Clinical results in 12 weeks, tenderness joint count is average 3.71 0.8 down from to, the swollen joint count average 3.29-0.8, DAS28-ESR achieved average 2.45 and remission. Also mHAQ functional impairment declined from the Administration before average 0.90 average 0.13. 2 weeks early from MMP-3 (ng/ml) doses before average 406.1 average 178.2 from drops. CZP without MTX combined to even the onset of clinical effect quickly, can achieve remission at week 12 were in effect.

## P2-082

### Effectiveness of Adalimumab (ADA) for rheumatoid arthritis (RA) - Outcome of 4 years treatment -

Kosaku Oda

Department of Orthopedic Surgery, Takatsuki Red Cross Hospital

Conflict of interest: None

**[Purpose]** Clinical assessment of ADA treatment for 4 years in RA patients. **[Objective]** 16 patients (Pts) were subjected to the assessment of ADA treatment for 4 years from August 2008. Average age was 60.5 yrs (39-70), disease duration was 10.4 years (1.3 to 38) and male/female ratio was 1/15. PSL combination rate was 73.1% in average dose of 4.84mg, and MTX combination rate was 100 % with the average dose of 7.31mg/wk. Biologics history included 20 Pts of bio-naïve and 7 Pts of switch (IFX 3 Pts and ETN 2 Pts). **[Results]** Retention rate was 75.0% after 4 years and four Pts were discontinued (side effects and bio-free remission). After 4 years treatment with ADA, average DAS28 (CRP) was improved from 4.97 to 1.95, and DAS28 remission rate reached to 93.8% (bio-naïve group was 100% and switch group was 80.0%, respectively). **[Conclusion]** ADA administration showed a high efficacy and retention rate at 4 years.

## P2-083

### The efficacy and safety of certorizumab pegol in patients with rheumatoid arthritis

Naoki Kondo, Junichi Fujisawa, Naoko Kudo, Naoto Endo

Division of Orthopaedic Surgery, Department of Regenerative and Transplant Medicine, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Conflict of interest: None

**[Objective]** To examine the short term results of certorizumab pegol (CZP) in patients with RA. **[Methods]** CZP was introduced to 11 RA patients in our outpatient clinic. All were female, 58 years old on average (43 to 74 year-old), RA duration was 7.1 years on average (5 months to 29 years). Follow up duration was 7.2 months on average (1 to 16 months). Four cases were bio-naïve and the other 7 cases were treated by any biologics. Etanercept was used in 6 and adalimumab was used in 1 as biologics just before CZP introduction. The efficacy and safety of CZP were evaluated. **[Results]** CZP was continued in 8 cases. In these cases, average of disease activity score 28 (DAS28) was 4.86 just before CZP introduction, 3.87 at 1.5 months (just after loading phase), 3.71 at 3 months, and 3.07 at 6 months. Moderate response was shown in 7, and no response was in 4. Of 3 discontinuation cases, 1 case (moderate response) was due to pain on injection. The other 2 cases were due to no response. Out of 5 cases of high disease activity on DAS28, CZP was continued in 4 cases. No severe adverse event was detected. Drug eruption was shown in 1 case. **[Conclusions]** After CZP administration, DAS28 was decreased within 6 months. These data suggest that CZP is effective in refractory RA patients.

## P2-084

### Remarkable improvement of a knee joint lesion in a patient with rheumatoid arthritis after golimumab therapy: a case report

Kunio Yamada, Kaneaki Tawada, Hideki Muro, Keisuke Hoshino, Shinji Funahashi, Makoto Fukuta, Hidetoshi Iwata  
Department of Orthopaedic Surgery, Komaki City Hospital

Conflict of interest: None

[Objectives] We report a case in which a knee joint lesion improved remarkably after golimumab therapy. [Case] A 62-year-old man with a 15-year history of rheumatoid arthritis was referred for total knee arthroplasty (TKA) and a change in medication, owing to progressive destruction of the left knee joint despite methotrexate. The 28-joint disease activity score using C-reactive protein (DAS28-CRP) was 4.51. We recommended TKA owing to severe pain and joint destruction of the knee, but the patient requested biologics. Four-weekly subcutaneous injections of 50 mg golimumab were started. The pain and swelling disappeared quickly. The DAS28-CRP decreased to 1.72 after 2 years of therapy. The Japanese Orthopedic Association score improved from 41 to 85. Radiographic knee assessment showed improvement from Larsen grade IV to II, with repair of bony erosions and restoration of joint space. [Conclusion] Most hip and knee joints with moderate-to-advanced pre-existing damage show radiographic progression even after anti-TNF therapy due to the mechanical stress of weight-bearing. In this rare case, structural knee joint damage was repaired after golimumab therapy, and TKA became unnecessary.

## P2-085

### Usefulness of golimumab for routine clinical out-patient treatment

Megumi Matsuhashi, Akemi Kitano, Jun Fukae, Yuko Aoki, Mihoko Henmi, Fumihiko Sakamoto, Akihiro Narita, Hisanori Takamatsu, Takeya Ito, Akio Mitsuzaki, Masato Isobe, Masato Shimizu, Kazuhide Tanimura  
Hokkaido Medical Center for Rheumatic Diseases

Conflict of interest: None

At the authors' hospital, golimumab (GL) has been used to treat 73 RA patients to date. The usefulness of this treatment was analyzed, and the findings are reported here. The mean age of the 73 patients was 57.9 years, and approximately 40% were over 65. Approximately 80% of patients were concomitantly administered MTX, and 66% of the total received MTX < 8 mg/week; and approximately 50% of the patients received MTX < 8 mg/week were administered 100 mg of GL. In the evaluation of efficacy on the basis of DAS28, GL was found to be effective within 4 weeks after administration, whether as monotherapy or in combination with MTX, and irrespective of MTX dose. In particular, when 100 mg of GL was administered, MTX was effective even at low dose. In addition, evaluation of the severity of inflammation by joint echography showed efficacy irrespective of MTX dose. A large proportion of patients showing high disease activity on the basis of DAS28 score were administered 100 mg of GL, but marked alleviation was found by week 4. For a first-line biological agent to be used in combination with MTX at any dose, it is important to consider the option of GL. In addition, the regimen of once-monthly subcutaneous injection makes GL very convenient for patients.

## P2-086

### Retention rate of adalimumab treatment in our hospital

Akiko Suda, Toshiyuki Watanabe, Shigeru Ohno, Yoshiaki Ishigatsubo  
Center for Rheumatic Disease, Yokohama City University

Conflict of interest: None

[Objectives] The retention rates of treatment with abatacept (ADA) were evaluated in our institution. [Methods] A total of 63 patients who started ADA therapy were evaluated. [Results] Twenty four patients had received at least one biological agent before ADA therapy. Thirty nine patients received monotherapy. Treatment retention rates were 77.4%, 75.6%, and 57.5% at weeks 24, 52 and 104, respectively. A total of 4 adverse events occurred. Analysis of patients by factors possibly affecting retention rates revealed no significant differences by patient characteris-

tics. [Conclusion] We conclude that ADA is a beneficial drug in our hospital.

## P2-087

### Examination of the clinical effect predictive factor of Golimumab 100mg

Hiroshi Harada, Takaaki Morooka, Masaaki Morooka  
Morooka Orthopedic Hospital Rheumatic Disease Center

Conflict of interest: None

[Objectives] About 26 Golimumab (GLM) 100mg medication RA patients, the factor which influences validity was examined using after-medication 52-week clinical data. [Methods] It judged effective with the LOCF method that the case in which both of the improvement of DAS28-ESR $\geq$ 1.2 and DAS28-ESR $\leq$ 3.2 at 52-week were filled, and divided into two groups by the existence of validity. Correlation with the patient background of a baseline and validity is considered. [Results] The persistence rate was 80.7% (effective group: 91.7%, invalid group: 71.4%), and the reason for a stop was effect insufficient of three patients (11.5%), adverse event of one patient (3.8%), and economic reason of one patient (3.8%). They were 12 effective groups and 14 invalid groups among 26 patients. The factors with correlation with validity were weight (54.6kg vs 64.2kg), BMI (22.61 vs 25.12), anti-CCP antibody (131.1U/ml vs 282.6U/ml), RF (135.1 U/ml vs 213.3 U/ml), and the number of BIO (s) used before. Correlation was not observed at stage, class, the dose of MTX, the dose of PSL, DAS, SDAI, MMP3, mTSS, HAQ, age, and disease duration. [Conclusion] In order to obtain validity by GLM100mg, it is necessary to care about weight, BMI, anti-CCP antibody level, RF value, and the number of BIO (s) used before.

## P2-088

### Repair and progression of bone erosion in a rheumatoid arthritis patient with infliximab

Takashi Imagama, Atsunori Tokushige, Kazushige Seki, Toshihiko Taguchi  
Department of Orthopedic Surgery, Yamaguchi University School of Medicine, Ube, Japan

Conflict of interest: None

[Objectives] We report our case which progression and repair of the joint destruction to the PIP joints of fingers by infliximab (IFX) occurred at the same time. [Methods&Results] The case is 63 years old, a woman. DAS28-CRP was 2.88 and power doppler showed positive findings of Grade1 to the right ring finger, left middle finger PIP joints in ultrasonography. X-rays showed the joint space narrowing in PIP joints of right ring and left middle fingers and the bone erosion in left middle finger. At 3 months after IFX administration, DAS28-CRP was 2.21 and the symptom and power doppler signal of the left middle finger was disappeared, but the findings remained in only right ring finger. One year after IFX, the left middle finger PIP joint recognized repair of the bone erosion, but bone erosion appeared to the right ring finger. [Conclusion] It is reported that improvement of the disease activity is greatly associated with the suppression and the repair of joint destruction. However, in our case the progress of the joint destruction occurred in the left joint of symptoms even if improvement of the disease activity was obtained. It is necessary for us to make a treatment strategy with the goal of the symptom improvement of individual joints as well as disease activity.

## P2-089

### Prediction of remission rate at 1 year by early clinical response of certolizumab pegol in rheumatoid arthritis patients

Akito Nishimura, Youjiro Minegishi  
Shizuoka W.F.A.C. Shimizu-Kosei Hospital

Conflict of interest: None

[Objectives] To examine whether remission rate at 1 year (1y) is predictable or not by 12 weeks (12w) clinical response with certolizumab pegol (CZP) treatment in rheumatoid arthritis (RA) patients. [Methods]

RA patients who had CZP treatment over 1y at our hospital were eligible for analysis. Remission rate at 1y was analyzed based on the 12w response either DAS28 (ESR)  $\geq \Delta 1.2$  or DAS28 (ESR)  $< \Delta 1.2$ . [Results] 17 patients were subjected to the analysis. 13 were switch and 4 were naïve. 9 were concomitant use with MTX and CZP, whereas 4 were CZP monotherapy. 12 (70.5%) achieved DAS28 (ESR)  $\geq \Delta 1.2$  at 12w, and 5 (29.5%) were DAS28 (ESR)  $< \Delta 1.2$ . After 1y of treatment, remission was achieved in 5 (41.7%) in DAS28 (ESR)  $\geq \Delta 1.2$  group. 1 (20%) with DAS28 (ESR) response of  $< 1.2$  at 12w achieved remission. Switch subgroup were further analyzed. 8 (61.5%) achieved DAS28 (ESR)  $\geq \Delta 1.2$  at 12w, and 5 (38.5%) were DAS28 (ESR)  $< \Delta 1.2$ , and remission was achieved in 3 (37.5%) in DAS28 (ESR)  $\geq \Delta 1.2$  group, and 1 (20%) with a DAS28 (ESR) response of  $< 1.2$  at 12w achieved remission. [Conclusion] We suggest that an early response to CZP at 12w as measured by DAS28 (ESR) changes could be a useful assessment to predict long term treatment outcome to achieve remission in daily practice. [Conflict of interest] None

## P2-090

### The investigation of patients treated with Infliximab (IFX) in Akita Registry in 2014

Toshiaki Aizawa<sup>1</sup>, Seiya Miyamoto<sup>2</sup>, Yoichi Kataoka<sup>3</sup>, Masaaki Ogino<sup>4</sup>, Hiromi Morita<sup>5</sup>, Kunitaka Yang<sup>6</sup>, Wataru Watanabe<sup>7</sup>, Nobuhiro Ishizawa<sup>9</sup>, Kazuhiro Shoji<sup>11</sup>, Natsuo Konishi<sup>12</sup>, Hidetoshi Watanabe<sup>16</sup>, Takeshi Kashiwagura<sup>13</sup>, Masakazu Urayama<sup>14</sup>, Hiroki Ito<sup>15</sup>, Tsutomu Sakuraba<sup>17</sup>, Moto Kobayashi<sup>17</sup>, Keiji Kamo<sup>18</sup>, Hiroshi Aonuma<sup>19</sup>, Yusuke Sugimura<sup>10</sup>, Naohisa Miyakoshi<sup>8</sup>, Yoichi Shimada<sup>8</sup>

<sup>1</sup>Department of Orthopedic Surgery, Kitaakita Municipal Hospital, Akita, Japan, <sup>2</sup>Department of Orthopedic Surgery, Nakadori General Hospital, Akita, Japan, <sup>3</sup>Joto Orthopedic Clinic, Akita, Japan, <sup>4</sup>Department of Orthopedic Surgery, Koto General Hospital, Akita, Japan, <sup>5</sup>Morita Orthopedic Clinic, Akita, Japan, <sup>6</sup>Yan Orthopedic Clinic, Akita, Japan, <sup>7</sup>Department of Orthopedic Surgery, Honjo Daiichi Hospital, Akita, Japan, <sup>8</sup>Department of Orthopedic Surgery, Akita University Graduate School of Medicine, Akita, Japan, <sup>9</sup>Department of Orthopedic Surgery, Fujiwara Memorial Hospital, Akita, Japan, <sup>10</sup>South Akita Orthopedic Clinic, Akita, Japan, <sup>11</sup>Shoji Orthopedic Clinic, Akita, Japan, <sup>12</sup>Department of Orthopedic Surgery, Akita Kousei Medical Center, Akita, Japan, <sup>13</sup>Department of Rehabilitation Medicine, Akita City Hospital, Akita, Japan, <sup>14</sup>Department of Orthopedic Surgery, Ogachi Central Hospital, Akita, Japan, <sup>15</sup>Department of Orthopedic Surgery, Yamamoto Kumiai General Hospital, Akita, Japan, <sup>16</sup>Watanabe Orthopedic Clinic, Akita, Japan, <sup>17</sup>Department of Orthopedic Surgery, Hiraka General Hospital, Akita, Japan, <sup>18</sup>Department of Orthopedic Surgery, Akita Rosai Hospital, Akita, Japan, <sup>19</sup>Department of Orthopedic Surgery, Kakunodate Municipal Hospital, Akita, Japan

Conflict of interest: None

[Objectives] To investigate the patients treated with Infliximab (IFX) who registered with the Akita Orthopedic group on Rheumatoid Arthritis (AORA). [Methods] One hundred and twenty-four patients were treated with IFX who registered with AORA in 2014. They were comprised the subjects of the present study. [Results] The patient characteristics were as follows: there were 25 males and 99 females, the mean age was 64 years (range 24-85 yr) and the mean disease duration was 197 months (5-837 months). IFX had been administered with a mean duration of 37 months (0-112 months). One hundred and three patients had been prescribed methotrexate (MTX) with a mean dose of 7.0 mg, and 61 patients had been prescribed a steroid (PSL) with a mean dose of 3.8 mg. The DAS28-ESR (4) could be calculated in 113 patients, and the mean was 2.74. Forty-six patients could continue IFX treatment during the investigation. MTX was prescribed in all patients with a mean dose of 7.0 mg, and PSL was prescribed in 21 patients with a mean dose of 3.4 mg. The mean DAS28-ESR (4) was 2.86 as calculated in 44 patients. Seventy-eight patients could not continue IFX treatment during the investigation. They were unable to continue IFX treatment, because of a decreasing effect, lung disease, financial reasons and so on.

## P2-091

### Two cases of long-term suppression effect to weight-bearing joint destruction by anti-TNF therapies for rheumatoid arthritis

Takahito Yamasaki, Yoshiki Okuda, Kensuke Kido, Hiromi Kondo,

Satoshi Inoue, Akira Adachi, Torao Kusakabe  
Department of Orthopedics Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan

Conflict of interest: None

[Case reports] Patient 1 was a 50-year-old female, Stage 3 Class 2. Bilateral hip joints were destroyed despite using MTX 8mg for 4 years. After 5 years from onset, we administered infliximab at Larsen grade III. 1 year later, the X-rays have shown sclerotic changes on subchondral bone. 2 years later, the osteophyte was made at left acetabular rim, and joint space was widened slightly. 10 years later, bilateral joints spaces were maintained in the same range. Patient 2 was a 67-year-old female, Stage 3 Class 2. Ankle joint space narrowing has progressed and bilateral joint have totally destroyed despite using MTX 10mg for 7 years. After 13 years from onset, we administered etanercept. 8 years later, joint spaces were widened to Larsen grade III. [Discussion] Due to the mechanical stress the weight-bearing joint is less likely to repair by biologics compared to non-weight. There is a report that even in patients with good response, hip and knee joints over Larsen grade III are hard to repair. Because patient 1 was relatively young, osteoarthritic change has occurred in early phase that lead to maintain the joint spaces. The joint spaces were widened to Larsen grade III in patient 2. There is a report that ankle joints are more likely to be restored unlike hip and knee joints.

## P2-092

### One-Year Continuation Rate of Golimumab for Patients with Rheumatoid Arthritis in our Clinic

Hideki Saito, Haruki Takagi, Kazutaka Takatsuka, Toshiyuki Kitaori, Yoshihiro Araki, Mitsuru Soen  
Fukui Red Cross Hospital, Fukui, Japan

Conflict of interest: None

[Objectives] We investigated the continuation rate and efficacy on patients with rheumatoid arthritis (RA) treated with Golimumab (GLM). Bio-naïve group and Bio-switch group were compared. [Methods] Among 34 RA patients who were treated with GLM, TJC28, SJC28, patient's global assessment (PtVAS), CRP, ESR, DAS28-ESR and SDAI were evaluated about 29 patients (9 Bio-naïve patients including 6 female, 20 Bio-switch patients including 18 female). mean age: 65.5 $\pm$ 11.7, mean disease duration: 9.70 $\pm$ 7.67years) who were treated with GLM followed during more than 52 weeks. [Results] The continuation rates of Bio-naïve and Bio-switch were 100%(9/9 cases) and 75%(15/20 cases) at 52 weeks individually. The use of MTX; Bio-naïve in 8 (88% mean dose 8mg/w), Bio-switch in 10 (50% mean dose 6.6mg/w) (p=0.046). The continuation rates of treatment with MTX and without MTX were 94%(17/18 cases) and 64%(7/11 cases) (p=0.033). Prior biologics; ADA 10, IFX 5, ETN 2, TCZ 2, ABT 1. GLM as second biologics 85%(17/20 cases), as more than third biologics 15%(3/20 cases). The continuation rates of GLM as second biologics tend to be better GLM as more than third biologics. [Conclusion] These results suggested that continuation rate on RA patients who were treated with GLM as Bio-naïve and Bio-switch during 52weeks.

## P2-093

### Effects of certolizumab pegol administration in bio-switch rheumatoid arthritis patients in daily clinical practice

Akito Nishimura, Youjiro Minegishi  
Shizuoka W.F.A.C. Shimizu-Kosei Hospital

Conflict of interest: None

[Objectives] To investigate the therapeutic outcome of certolizumab pegol (CZP) on the bio-switch rheumatoid arthritis (RA) patients. [Methods] 11 RA patients who had CZP treatment over 1 year at our hospital were eligible for analysis. Average age was 68.6 $\pm$ 15.5 and 7 were female, disease duration over 2 years was 8, 6 were over Stage III among the 11. 5 (45.5%) were CZP mono-therapy. Average number of the biological was 1.43 $\pm$ 0.51 and treatment period was 3.64 $\pm$ 1.82 years. Disease activities were evaluated with DAS28 (ESR) and SDAI after CZP initiation. [Results] Disease activity was improved after CZP treatment as

DAS28 (ESR) were changed from 5.2±1.1 to 3.7±1.0, 3.3±1.1, 3.4±1.8 through pretreatment CZP and 12w, 24w, 48w respectively. Similar trend was observed as SDAI were changed from 28.9±13 to 25.5±5.9, 14±12.2, 14.1±13.2 and 5 (45.5%) achieved low disease activity. CZP treatment have shown improvement of disease condition with or without MTX as SDAI was changed over 48w either with MTX (28.9±13 to 14±12.2) or without MTX (25.5±5.9 to 14.1±13.2). [Conclusion] CZP treatment showed early and good clinical outcome in the bio-switch RA patients and early improvement. Therapeutic effect was almost equivalent either presence or absence of MTX [Conflict of interest] None

## P2-094

### Profiles of patients in the Akita Orthopedic Group on Rheumatoid Arthritis registry who received adalimumab

Moto Kobayashi<sup>1</sup>, Seiya Miyamoto<sup>2</sup>, Natsuo Konishi<sup>3</sup>, Takeshi Kashiwagura<sup>4</sup>, Masakazu Urayama<sup>5</sup>, Tsutomu Sakuraba<sup>1</sup>, Hiroki Ito<sup>6</sup>, Toshiaki Aizawa<sup>7</sup>, Keiji Kamo<sup>8</sup>, Hiroshi Aonuma<sup>9</sup>, Yusuke Sugimura<sup>10</sup>, Masaaki Ogino<sup>11</sup>, Yoichi Kataoka<sup>12</sup>, Hiromi Morita<sup>13</sup>, Kunitaka Yang<sup>14</sup>, Wataru Watanabe<sup>15</sup>, Nobuhiro Ishizawa<sup>16</sup>, Kazuhiro Shoji<sup>17</sup>, Hidetoshi Watanabe<sup>18</sup>, Naohisa Miyakoshi<sup>19</sup>, Yoichi Shimada<sup>19</sup>

<sup>1</sup>Department of Orthopedic Surgery, Hiraka General Hospital, Akita, Japan, <sup>2</sup>Department of Orthopedic Surgery, Nakadori General Hospital, Akita, Japan, <sup>3</sup>Department of Orthopedic Surgery, Akita Kousei Medical Center, Akita, Japan, <sup>4</sup>Department of Rehabilitation Medicine, Akita City Hospital, Akita, Japan, <sup>5</sup>Department of Orthopedic Surgery, Ogachi Central Hospital, Akita, Japan, <sup>6</sup>Department of Orthopedic Surgery, Yamamoto Kumiai General Hospital, Akita, Japan, <sup>7</sup>Department of Orthopedic Surgery, Kita Akita Municipal Hospital, Akita, Japan, <sup>8</sup>Department of Orthopedic Surgery, Akita Rosai Hospital, Akita, Japan, <sup>9</sup>Department of Orthopedic Surgery, Kakunodate Municipal General Hospital, Akita, Japan, <sup>10</sup>South akita Orthopedic Clinic, Akita, Japan, <sup>11</sup>Department of Orthopedic Surgery, Koto General Hospital, Akita, Japan, <sup>12</sup>Joto Orthopedic Clinic, Akita, Japan, <sup>13</sup>Morita Orthopedic Clinic, Akita, Japan, <sup>14</sup>Yang Orthopedic Clinic, Akita, Japan, <sup>15</sup>Department of Orthopedic Surgery, Honjo Daiichi Hospital, Akita, Japan, <sup>16</sup>Fujiwara Memorial Hospital, Akita, Japan, <sup>17</sup>Shoji Orthopedic Clinic, Akita, Japan, <sup>18</sup>Watanabe Orthopedic Clinic, Akita, Japan, <sup>19</sup>Department of Orthopedic Surgery, Akita University Graduate School of Medicine, Akita, Japan

Conflict of interest: None

[Objectives] This study aimed to investigate the profiles of rheumatoid arthritis patients who received adalimumab (ADA). [Methods] We evaluated 50 patients in the Akita Orthopedic Group on Rheumatoid Arthritis (AORA) registry (mean age, 60 years) who received ADA. [Results] The mean disease period was 11 years. The cases had Steinbrocker classification stages I/II/III/IV (11/17/11/21 patients), classes 1/2/3/4 (13/28/8/1 patients). Forty-five patients (90%) received methotrexate (MTX; mean dosage, 7.3 mg/week); and 36 (72%), prednisolone (4.3 mg/day). The mean DAS28CRP (4) was 3.30 in the first ADA administration. The mean follow-up period was 97 weeks. The cumulative continuation rates were 86%(1 year), 73%(2 years), and 65%(3 years) in the Kaplan-Meier analysis. Fifteen patients (38%) had failure of ADA administration. Therapy was discontinued because of primary failure in 5 cases and secondary failure in 8. The mean disease activity score was 1.71, and 34 patients (68%) had good response in the final examination according to the criteria of the European League against Rheumatism. [Conclusion] The patients who received ADA had a high combination rate with MTX, high continuation rate, and good results, and were therefore appropriately selected and treated.

## P2-095

### The efficacy of Golimumab to RA patients for short-term results

Taisei Kawamoto<sup>1</sup>, Satoshi Iida<sup>1</sup>, Takeshi Umibe<sup>2</sup>

<sup>1</sup>Department of Orthopaedics, Matsudo City Hospital, Japan, <sup>2</sup>Department of Rheumatology, Matsudo City Hospital, Japan

Conflict of interest: None

[Objectives] To evaluate Golimumab (GLM) to RA patients. [Methods] From April 2012, ten cases treated with GLM were evaluated by recording DAS28 (4/ESR). [Results] The average amount of GLM was

60mg. Results: DAS28 was 4.5 and decreased to 2.3 at 24 weeks, CRP was also reduced from 1.1 to 0.6. [Conclusion] The therapy of GLM was effective for short-term results.

## P2-096

### Investigation of Etanercept using the Akita Orthopedic Group on Rheumatoid Arthritis (AORA) registry

Hiroshi Aonuma<sup>1</sup>, Seiya Miyamoto<sup>3</sup>, Yoichi Kataoka<sup>4</sup>, Masaaki Ogino<sup>5</sup>, Hiromi Morita<sup>6</sup>, Kunitaka Yang<sup>7</sup>, Wataru Watanabe<sup>8</sup>, Nobuhiro Ishizawa<sup>9</sup>, Kazuhiro Shoji<sup>10</sup>, Natsuo Konishi<sup>11</sup>, Takeshi Kashiwagura<sup>12</sup>, Toshiaki Aizawa<sup>13</sup>, Hiroki Ito<sup>14</sup>, Masakazu Urayama<sup>15</sup>, Hidetoshi Watanabe<sup>16</sup>, Tsutomu Sakuraba<sup>17</sup>, Moto Kobayashi<sup>17</sup>, Keiji Kamo<sup>19</sup>, Yusuke Sugimura<sup>18</sup>, Naohisa Miyakoshi<sup>2</sup>, Yoichi Shimada<sup>2</sup>

<sup>1</sup>Department of Orthopedic Surgery, Kakunodate Municipal Hospital, Akita, Japan, <sup>2</sup>Department of Orthopedic Surgery, Akita University Graduate School of Medicine, Akita, Japan, <sup>3</sup>Department of Orthopedic Surgery, Nakadori General Hospital, Akita, Japan, <sup>4</sup>Joto Orthopedic Clinic, Akita, Japan, <sup>5</sup>Department of Orthopedic Surgery, Koto Kousei Hospital, Akita, Japan, <sup>6</sup>Morita Orthopedic Clinic, Akita, Japan, <sup>7</sup>Yan Orthopedic Clinic, Akita, Japan, <sup>8</sup>Department of Orthopedic Surgery, Honjo Daiichi Hospital, Akita, Japan, <sup>9</sup>Department of Orthopedic Surgery, Fujiwara Memorial Hospital, Akita, Japan, <sup>10</sup>Shoji Orthopedic Clinic, Akita, Japan, <sup>11</sup>Department of Orthopedic Surgery, Akita Kousei Medical Center, Akita, Japan, <sup>12</sup>Department of Rehabilitation Medicine, Akita City Hospital, Akita, Japan, <sup>13</sup>Department of Orthopedic Surgery, Kita Akita Municipal Hospital, Akita, Japan, <sup>14</sup>Department of Orthopedic Surgery, Yamamoto Kumiai General Hospital, Akita, Japan, <sup>15</sup>Department of Orthopedic Surgery, Ogachi Central Hospi, Akita, Japan, <sup>16</sup>Watanabe Orthopedic Clinic, Akita, Japan, <sup>17</sup>Department of Orthopedic Surgery, Hiraka General Hospital, Akita, Japan, <sup>18</sup>South Akita Orthopedic Clinic, Akita, Japan, <sup>19</sup>Department of Orthopedic Surgery, Akita Rosai Hospital, Akita, Japan

Conflict of interest: None

[Objectives] To investigate trends among patients using etanercept (ETN) from the AORA registry. [Methods] Background at the initiation of treatment, treatment continuation rate, and treatment effects were investigated for a total of 266 patients (females, 81.9%; mean age at initiation of treatment, 59 years; mean duration of illness, 11.3 years; mean PSL dose, 5.6 mg; mean CRP level, 2.68 mg/dl; mean MMP-3 level, 230.6 ng/ml) given ETN who were registered before the end of July 2014. [Results] DAS28-CRP was able to be assessed at the initiation of treatment for 197 patients (mean score, 4.58). The cumulative ETN continuation rate was 87.8% and 67.2% after one and five years, respectively. ETN was discontinued in 65 of 237 patients; the main reasons included insufficient response (n=27), adverse events (n=19). ETN was continued in 172 of 237 patients (mean continuation period, 3.6 years). Among patients continuing ETN, the mean PSL dose had been reduced to 3.6 mg at the time of the final survey, with reductions in CRP and MMP-3 to a mean of 1.87 mg/dl and 88.2 ng/ml, respectively. DAS28-CRP decreased to a mean of 2.42, and was <2.3 in 51.9% of patients. [Conclusion] We reported trends among patients using ETN from the AORA registry.

## P2-097

### Shortening infliximab infusion time in patients with rheumatoid arthritis influence did not influence on clinical results

Muneki Abe, Naohide Takigawa, Hisako Eshiro, Atsushi Fukai  
Nishinomiya Kyoritsu Neurosurgical Hospital

Conflict of interest: None

[Objectives] Present study aimed to assess the incidence of infusion reactions and clinical results in patients with rheumatoid arthritis receiving 1-hour infliximab (IFX) infusions. [Methods] The infusion time was reduced to 1 hour in patients with rheumatoid arthritis treated at least 3 times with 2-hour infusion of IFX without infusion reactions. [Results] Fifteen patients (1 male and 14 females, mean age: 61.7±10.5 years) were treated with 1-hour infliximab infusion. Overall, 1-hour infusion was 124 times. The incidence of infusion reaction was 13% (2/14 patients) and 1.6% (2/124 times). Two patients whose blood pressure lowered had no subjective symptoms at the time of lowering the blood pressure. MMP-3 before reducing the infusion time was 42.1 ± 15.6 and that of after reduc-



ing the infusion time was  $46.5 \pm 28.2$ . DAS28-CRP was  $2.36 \pm 0.58$  and  $2.18 \pm 0.57$ , respectively. There were no significant differences. [Conclusion] The infusion time of IFX can be safely reduced and there was no influence on clinical results.

## P2-098

### A study of the clinical efficacy and the persistency ratio of golimumab in patients with rheumatoid arthritis

Kazuo Kamada, Kazuhiko Higashioka, Kenji Yoshida, Kensuke Oryoji, Shinichi Mizuki, Eisuke Yokota  
Matsuyama Red Cross Hospital, the Center for Rheumatic Disease

Conflict of interest: None

In this study, we analyzed the clinical efficacy and the persistency ratio in 45 patients with rheumatoid arthritis treated with golimumab (Simpsoni, an anti-TNF antibody) from December 2011 to September 2010 in our hospital. The persistency ratio at 52 weeks was 76.7% in all. 5 of 8 patients with failure were effected insufficiency. The persistency ratio at 52 weeks was 82.5% on the group with MTX versus 57.1% on the group without MTX. And it was 79.3% on the group for first biologics versus 71.5% on the group for second/third biologics. In addition, by the dose distinction, it was 77.7% on the group with 50mg of administration versus 76.4% on the group with 100mg of administration. Improvement of bone erosion was showed on one case with 100mg of administration. Golimumab may be used safely relatively and effectively biologics

## P2-099

### Long-term therapeutic outcomes over 10 years with infliximab at our institution

Makoto Inoue, Tetsuya Kaneko, Yasuyuki Tamura, Hiroshi Inoue  
Inoue Hospital

Conflict of interest: None

Objective: To investigate the long-term (10-year) therapeutic outcomes of infliximab treatment for rheumatoid arthritis (RA) at our institution. Subjects and Methods: Continuation rates, reasons for discontinuation, and other characteristics were investigated in 93 patients treated with infliximab at our hospital after its initial release onto the market. C-reactive protein (CRP) levels, joint tenderness and swelling, and disease activity score 28-CRP were investigated year by year in patients who received at least 7 years of continuous treatment (n=35). Results: Year-on-year improvements were observed for all data items in patients receiving long-term treatment. Furthermore, remission was maintained in patients who achieved early remission. Discussion: Long-term treatment with infliximab appeared to enable long-term control of RA without diminished effects.

## P2-100

### Clinical experience and positioning of certolizumab institution in 29 RA patients from a single institution

Masato Shimizu, Jun Fukae, Akihiro Narita, Akemi Kitano, Masato Isobe, Megumi Matsuhashi, Akio Mitsuzaki, Kazuhide Tanimura  
Hokkaido Medical Center for Rheumatic Diseases

Conflict of interest: None

[purpose] We report on 29 RA patients treated by Fc-free Pegylated TNF inhibitor; Certolizumab at our institution. [method] Eligible patients had failed prior conventional DMARDs or desired pregnancy. 9 patients (31%) were long-established RA. We were used, and MTX was most common with 49% with the combined medicine (DMARD) nine (31%) for a first-line drug with the breakdown of the administration, and the single administration was performed in 24%, too. [results] the parameter (DAS28, SDAI, CDAI) until 24 weeks was significantly improved. and the difference between the groups was found neither alone in group, the MTX combination group, the IGU combination group. Remission rates maintained around 20%. There was the improvement of the blood flow signal in the joint echo early and maintained the effect over 24 weeks. [conclusions] Certolizumab showed rapid onset of efficacy

in biologics-naïve patients, and there was a small number of second treatment-failures. Certolizumab showed efficacy regardless of concomitant MTX. Certolizumab showed efficacy even in second or third-line treatment.

## P2-101

### Effect of certolizumab pegol on human monocytes

Takayuki Hoshiyama, Yuko Sakuma, Yoshiyuki Arinuma, Tatsuo Nagai, Shunsei Hirohata  
Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan

Conflict of interest: None

[Objectives] Certolizumab pegol (CZP) is an agent which comprises humanized anti-TNF- $\alpha$  monoclonal antibody Fab' fragment linked to polyethylene glycol (PEG). The current study was undertaken to explore the direct effect of CZP on human monocytes. [Methods] Monocytes were purified from peripheral blood mononuclear cells obtained from healthy donors using magnetic beads. Purified monocytes were cultured in 24-well microtiter plates with CZP, IFX, control IgG, or PEG at pharmacological attainable concentration. After 24 hours, the supernatants were replaced with culture medium without TNF inhibitors, control IgG or PEG, followed by the addition of LPS. After additional 24 hours of incubation, the supernatants were assayed for TNF- $\alpha$  and IL-6. CZP or IFX was incubated with recombinant TNF- $\alpha$  for 2 hours, then the concentrations of TNF- $\alpha$  in the mixture were measured. [Results] The concentration of TNF- $\alpha$  and IL-6 in the supernatants of LPS-stimulated monocytes precultured with CZP was lower than that with PEG, and was as low as that with IFX. Neutralizing effect against the soluble TNF- $\alpha$  by CZP was more potent than that by IFX at the same concentration. [Conclusion] These results suggest that CZP might have some direct effects on monocytes in a manner that does not involve Fc receptors.

## P2-102

### Periodontal and serum protein profiles before and after medication with adalimumab

Tetsuo Kobayashi<sup>1,2</sup>, Satoshi Ito<sup>3</sup>, Daisuke Kobayashi<sup>3</sup>, Moe Okada<sup>2</sup>, Ichiei Narita<sup>4</sup>, Akira Murasawa<sup>3</sup>, Kiyoshi Nakazono<sup>3</sup>, Hiromasa Yoshie<sup>2</sup>  
<sup>1</sup>Niigata University Medical and Dental Hospital, Niigata, Japan, <sup>2</sup>Division of Periodontology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, <sup>3</sup>Niigata Rheumatic Center, Shibata, Japan, <sup>4</sup>Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Conflict of interest: None

[Objectives] Overproduction of TNF- $\alpha$  has been implicated as a common risk factor for RA and periodontitis. The aim of the present study is to compare periodontal and serum protein profiles in patients with RA before and after adalimumab (ADA) therapy. [Methods] Periodontal and rheumatologic parameters and serum cytokine levels were evaluated in 19 patients with RA treated with ADA at baseline and 3 months later. After two-dimensional SDS-PAGE, proteins with significant difference in abundance before and after ADA therapy were determined and identified with mass spectrometry and protein databases. [Results] The patients showed a significant decrease in periodontal inflammation and destruction levels, DAS28-CRP, and serum levels of RF, anti-CCP antibodies, MMP-3, IL-6, and TNF- $\alpha$  after ADA medication, although plaque levels were comparable. A total of five proteins were significantly decreased in abundance after ADA medication, which corresponds to acute-phase protein (serum amyloid A and alpha-1-acid glycoprotein) and complement components (complement factor H and complement component 4). [Conclusion] These results suggest an effect of ADA therapy on serum protein profiles, which may lead to an improvement of periodontal condition in patients with RA.

## P2-103

### SNP algorithms for prediction of remission, efficacy and adverse events of certolizumab-pegol (CZP)

Satoru Koyano<sup>1</sup>, Keiko Funahashi<sup>1</sup>, Takeshi Nakamura<sup>2</sup>, Takako Miura<sup>2</sup>,

Kosuke Okuda<sup>2</sup>, Tsukasa Matsubara<sup>2</sup>

<sup>1</sup>Research Institute of Joint Diseases, Kobe, Japan, <sup>2</sup>Matsubara Mayflower Hospital, Kato, Japan

Conflict of interest: None

[Objectives] We established SNP algorithms for prediction of remission or non-remission, responders or non-responders, and adverse events in CZP-treated patients. [Methods] 30 RA patients treated with CZP were included in this study. Remission or efficacy was assessed by DAS28 (CRP) at 48 weeks after the initial treatment. Any adverse events that may have been related to CZP administration and observed at 48 weeks of treatment were considered to be side effects. We selected 10 SNPs associated with CZP-responsiveness, remission, and adverse events ( $p < 0.0001$ ). We scored the relationship between each SNP and remission, efficacy or adverse events and estimated total score of 10 SNPs. [Results] Approximately 88-93% of remission or non-remission group could be determined by one algorithm. Similarly, 90-97% of efficacy could be determined by other algorithm. Similarly, 90-94% of adverse events plus or minus in CZP-treated group could be determined by other algorithm. [Conclusion] The SNP algorithm could be useful for prediction of remission, efficacy and adverse events before treatment with CZP.

## P2-104

### SNP algorithms for prediction of remission, efficacy and adverse events of golimumab (GOL)

Satoru Koyano<sup>1</sup>, Keiko Funahashi<sup>1</sup>, Takeshi Nakamura<sup>2</sup>, Takako Miura<sup>2</sup>, Kosuke Okuda<sup>2</sup>, Tsukasa Matsubara<sup>2</sup>

<sup>1</sup>Research Institute of Joint Diseases, Kobe, Japan, <sup>2</sup>Matsubara Mayflower Hospital, Kato, Japan

Conflict of interest: None

[Objectives] We established SNP algorithms for prediction of remission or non-remission, responders or non-responders, and adverse events in GOL-treated patients. [Methods] 33 RA patients treated with GOL were included in this study. Remission or efficacy was assessed by DAS28 (CRP) at 48 weeks after the initial treatment. Any adverse events that may have been related to GOL administration and observed at 48 weeks of treatment were considered to be side effects. We selected 10 SNPs associated with GOL-responsiveness, remission, and adverse events ( $p < 0.0001$ ). We scored the relationship between each SNP and remission, efficacy or adverse events and estimated total score of 10 SNPs. [Results] Approximately 90-94% of remission or non-remission group could be determined by one algorithm. Similarly, 92-98% of efficacy could be determined by other algorithm. Similarly, 88-95% of adverse events plus or minus in GOL-treated group could be determined by other algorithm. [Conclusion] The SNP algorithm could be useful for prediction of remission, efficacy and adverse events before treatment with GOL.

## P2-105

### Successful delivery and re-remission-induction by reuse of Tocilizumab to treat amyloid A amyloidosis complicating juvenile idiopathic arthritis carry over case

Yasuaki Okuda, Makoto Onishi, Kenichiro Matoba, Kazuo Jouyama, Akihiro Yamada, Naoya Sawada, Yousuke Murata, Tomoyuki Mutoh, Kiyoshi Takasugi

Center for Rheumatic Diseases, Dohgo Spa Hospital, Ehime, Japan

Conflict of interest: None

[Background] There is no case report which used Tocilizumab (TCZ) during pregnancy so far. We report successful deliver and outcome by re-using TCZ to treat amyloid A amyloidosis (AA) complicating juvenile idiopathic arthritis (JIA) carry over case. [Case report] 35 yr., female. The patient was diagnosed JIA by presenting high fever, lymphadenopathy, hepatosplenomegaly and arthritis at 14. She was treated with moderate dose of prednisolone (PSL) and high dose of methotrexate and so on. But high inflammatory state continued. She developed AA by GI symptoms at 22 and renal symptoms subsequently. TCZ was administered by compassionate use at 24 and then her arthritis and AA symptoms became in

remission. Although sequential evaluations of AA deposits and quantifications decreased to a large degree, low amount of AA still remained. She became pregnant at 34 and TCZ was stopped. But after 60 days from quit of TCZ, she had a relapse and the level of SAA highly elevated. We administered 10 mg of PSL, but high level of SAA and arthritis continued. Therefore we reused TCZ subcutaneously, her arthritis disappeared and the level of SAA was normalized subsequently. Although she gave birth prematurely, she had a child without anomaly. This case suggested a benefit of use of TCZ during pregnancy.

## P2-106

### Tocilizumab and pregnancy: Four experiences with pregnancy in RA patients receiving Tocilizumab therapy

Kayoko Kaneko, Mikako Goto, Atsuko Murashima

Division of Maternal Medicine, Center of Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, Tokyo, Japan

Conflict of interest: None

[Introduction] We present 4 cases of women with rheumatoid arthritis (RA) exposed to tocilizumab (TCZ) before and at the time of conception. [Case1] A-31-year-old woman with RA refractory to etanercept (ETN) became pregnant 2 months after starting TCZ. It has discontinued when her pregnancy was confirmed and she delivered a healthy full-term newborn. [Case2] A-38-year-old woman with RA refractory to ETN, adalimumab and golimumab (GLM) became pregnant 8 months after starting TCZ. It has discontinued as soon as her pregnancy was confirmed and ETN was prescribed again from 10 weeks in gestation. She had no complication except for deterioration of chronic hypertension. [Case3] A-42-year-old woman with RA refractory to ETN, infliximab and GLM became pregnant 15 months after starting TCZ. It has discontinued at 3 week's gestation. However, she had a miscarriage because of partial hydatidiform mole at 11 weeks. [Case4] A-30-year-old woman with RA refractory to GLM became pregnant 11 months after starting TCZ. It has discontinued when her pregnancy was confirmed and she had no complication until 17 weeks. [Conclusion] The TCZ therapy could be a good alternative to conventional medication for RA patient who is desire to bear child and whose symptom is hard to control with TNF blockers.

## P2-107

### Preserved renal function in two patients with systemic AA amyloidosis secondary to RA

Toshiharu Ueno<sup>1</sup>, Ryo Hazue<sup>1</sup>, Akinari Sekine<sup>1</sup>, Koki Mise<sup>1</sup>, Masahiro Kawada<sup>1</sup>, Keiichi Sumida<sup>1</sup>, Rikako Hiramatsu<sup>1</sup>, Eiko Hasegawa<sup>1</sup>, Noriko Hayami<sup>1</sup>, Tatsuya Suwabe<sup>1</sup>, Junichi Hoshino<sup>1</sup>, Naoki Sawa<sup>1</sup>, Kenmei Takaichi<sup>1</sup>, Yoshifumi Ubara<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Toranomon Hospital, <sup>2</sup>Department of Pathology, Toranomon Hospital

Conflict of interest: None

[Objectives] [Methods] Two patients with systemic AA amyloidosis secondary to RA treated with several biologic agent. [Results] Long-term preservation of renal function were achieved in two all patients. [Conclusion] Biological agents can not only ameliorate the activity of RA but also effective for preferable renal outcome.

## P2-108

### Tocilizumab (TCZ) was effective to the rheumatoid arthritis (RA), which showed the symptoms of Methotrexate (MTX) pneumonia during Golimumab (GLM) and MTX medication

Akinori Ito<sup>1</sup>, Keisuke Ota<sup>3</sup>, Jun Takeda<sup>2</sup>, Yuko Watanabe<sup>2</sup>, Sadakazu Torii<sup>1</sup>, Takeo Yoshinouchi<sup>1</sup>

<sup>1</sup>Toyokawa City Hospital, Toyokawa, Japan, <sup>2</sup>Toyokawa City Hospital, Toyokawa, Japan, <sup>3</sup>Toyokawa City Hospital, Toyokawa, Japan

Conflict of interest: None

[Objectives] We report the case who was treated Golimumab (GLM) and Methotrexate (MTX), was suffered from MTX pneumonia, but GLM

and MTX medication was stopped and she was kept remission by Tocilizumab (TCZ). [The case report] A case is a 71 years-old woman. She was diagnosed RA from 11 years ago. 2 years ago, She was introduced from local doctor because of CRP elevation. She started by MTX at April of the same year. MTX was increased from October. Since she had been suffering from CRP elevation and arthralgia, GLM was started at March 1 year ago (DAS28ESR 6.91). But she showed the symptom of pneumonia at May. She admitted the hospital at June, but soon left. However, She showed pneumonia and pleural effusion, therefore admitted the hospital again. Her pneumonia was recovered by mPSL pulse therapy. She left the hospital but old pneumonia was remained on X-ray. She re-medicated GLM but RA activity was high then changed to TCZ at October 30th. TCZ was really effective. Now, remission is maintained (DAS28ESR 1.84) [Conclusion] We diagnosed pneumonia by MTX, PSL therapy and Ceased MTX led to recovery of pneumonia. TCZ kept the remission on RA. We reported the Notes of the pneumonia on adverse effect of MTX.

## P2-109

### Contrast-enhanced MRI is helpful to judge-real remission-to discontinue biologics to patients who reached clinical remission by Tocilizumab: a case report

Hiroshi Yokoyama

Yokoyama Orthopedic, Nishinomiya, Japan

Conflict of interest: None

The Judgment to discontinue the biologics to RA patients, who reached clinical remission, is often difficult. We report the experience of one case that contrast-enhanced MRI was useful to this judgment. Patient was a 58 years old woman, weight 52kg. In December 2012, swelling was observed in the both ankle joints and both MTPs, and the tenderness was observed in both MTPs. The laboratory test was ESR 78 mm/hr, CRP 1.8 mg/dl, RF 4.8IU/ml, anti-CCP antibody 0.8U/ml, IL-6 3.96 pg/ml. Steinbrocker classification was Stage I. Arthritis was observed more than 6 weeks. Although EULAR/ACR classification criteria was 5 points, we strongly doubted RA, and started Salazosulfapyridine. After two months, we started tocilizumab (TCZ). MRI was carried out before TCZ. Synovitis was observed in MTPs. Bone marrow edema was observed in the second and third metatarsal epiphysis. First three months intravenous TCZ was used, and then switched to subcutaneous TCZ. Symptoms improved gradually and reached to CDAI remission. In August 2014, we confirmed that synovitis and bone marrow edema had disappeared by MRI. Contrast-enhanced MRI is possible to visualize the bone marrow edema and synovitis. MRI may help the judgment of the discontinuation of biologics to patients who reached clinical remission.

## P2-110

### Association between choice of agents and risk of serious infections in subjects of rheumatoid arthritis treated with biologic disease-modifying anti-rheumatic drugs

Atsushi Omoto, Aki Sakashita, Akiko Ido, Masatoshi Kadoya, Wataru Fukuda

Center for Rheumatic Disease, Japan Red Cross Kyoto Daiichi Hospital, Kyoto, Japan

Conflict of interest: None

[Objectives] To determine the risk of serious infection in patients with rheumatoid arthritis (RA) receiving biologic disease-modifying anti-rheumatic drugs (bDMARDs) and to identify factors that predict a higher risk. [Methods] This prospective cohort study included RA patients who treated with biologic DMARDs from March 2007 to October 2013 (n =942.25 patient years [PY]). Serious infections (Herpes zoster, Lower respiratory infection, Bone and soft tissue infection, urinary tract infection, severe enterocolitis) were enrolled and we evaluated the relation between choice of biologic agents and risk of serious infections. [Results] The risk ratio of herpes zoster infection for the group of using abatacept was significantly higher than the group of using other biologic DMARDs (8.6/PY vs 3.4/PY, p=0.02). The risk ratio of infection of the musculoskeletal system for the group of using Tocilizumab was significantly higher than the group for using other biologics DMARDs (5.8/PY vs 1.9/

PY, p<0.001). The risk ratio of hospitalization for the group treated with Tocilizumab was higher than the group treated with other biologic DMARDs (p<0.05). [Conclusion] Each biologic DMARDs has a characteristic trend for the risk of various infections.

## P2-111

### Treatment discontinuation factor, continuation rate of the biologic treatment in patients with rheumatoid arthritis

Tomoya Miyamura, Masataka Nakamura, Makiko Higuchi, Shoko Kodama, Soichiro Takahama, Yu Kaku, Rumi Minami, Masahiro Yamamoto, Eiichi Suematsu

Department of Internal Medicine and Rheumatology, Clinical Research Institute, National Hospital Organization, Kyushu Medical Center, Fukuoka, Japan

Conflict of interest: None

[Objectives] Biologic treatment for rheumatoid arthritis (RA) showed high effectiveness, but the problems of inefficacy and the side effects become clear. The objectives of this study is to clarify the treatment discontinuation factor, continuation rate of the biologic agent in patients with RA. [Methods] We examined patient background, discontinuation rate, discontinuation factors and disease activity in 139 RA patients who were introduced newly biological agent in our hospital from 2010 to 2014. [Results] Biologic agent was discontinued in 47 patients (remission 12, side effects 16, inefficacy 19) during an observation period, and the continuation rate of one year was 76.9%. The discontinuation reasons of side effects were three patients with infectious diseases, five with interstitial lung disease, three with malignancy, and five with others. The discontinuation patients with side effect or inefficacy showed significantly male, steroid combination, coexistence complications and high SDAI score after one month treatment in comparison with the continuation patients. [Conclusion] Our result revealed that biologic discontinuation was more likely in the patients with steroid combination, coexistence complications and high SDAI score after one month treatment.

## P2-112

### Efficacy and safety of non-TNF inhibitor biologics for elderly-onset rheumatoid arthritis

Kazuyuki Fujita<sup>1</sup>, Yoshihisa Nomura<sup>2</sup>, Yuriko Yamamura<sup>1</sup>, Noriya Momoki<sup>2</sup>, Keisuke Maruyama<sup>2</sup>, Akiko Ueno<sup>1</sup>, Tsuneto Onbe<sup>2</sup>, Masahiro Yamamura<sup>1</sup>

<sup>1</sup>Center for Rheumatology, Okayama Saiseikai General Hospital, Okayama, Japan, <sup>2</sup>Center for Kidney Diseases, Okayama Saiseikai General Hospital, Okayama, Japan

Conflict of interest: None

**Objectives:** To compare the efficacy and safety of non-TNF inhibitors for MTX-resistant and -intolerant patients with elderly-onset rheumatoid arthritis (EORA: onset>65 yo) with those of TNF inhibitors. **Methods:** 33 patients with EORA (16 women, median age 76.0 yo) had been treated with TNF inhibitors or non-TNF inhibitors (CTLA4-Ig or IL-6 inhibitors) since April 2011. The efficacy was determined by the induction rate of remission and low-disease activity (LDA) in treated patients using SDAI. **Results:** The rates of remission and LDA induction were more than 80% in EORA patients with CTLA4-Ig and IL-6 inhibitors at 3 month through 12 month, which were similar with the rates of TNF inhibitors. Adverse events have been observed similarly between non-TNF inhibitors and TNF inhibitors, but the number of events was lowest for CTLA4-Ig at present. **Conclusions:** TNF inhibitors, CTLA4-Ig, and IL-6 inhibitors showed similar efficacy and safety.

## P2-113

### The effect of abatacept on telomerase activity of lymphocytes of patients with rheumatoid arthritis

Kazuhiro Otani, Yosuke Oto, Masayuki Yoshiga, Haruyasu Ito, Kenichiro Hirai, Kentaro Noda, Taro Ukichi, Kazuhiro Furuya, Ken Yoshida, Isamu Kingetsu, Daitaro Kurosaka

Division of Rheumatology, Department of Internal Medicine, The Jikei University School of Medicine

Conflict of interest: None

**[Objectives]** Abatacept suppress the activation of T lymphocytes which are involved in pathogenesis of rheumatoid arthritis. And It was reported that telomerase activity of lymphocytes is upregulated when the lymphocytes are activated. Therefore we investigated effect of abatacept on telomerase activity of lymphocytes. **[methods]** This study included 16 patients with rheumatoid arthritis starting treatment of abatacept from August 2012 to August 2013. We collected their peripheral blood samples before starting abatacept, 4, 12, 24, and 52 weeks after the treatment. Then we measured telomerase activity of CD3 positive lymphocytes and CD19 positive lymphocytes by Telomeric Repeat Amplification Protocol (TRAP assay). **[results]** Mean age of patients was 59.2. DAS28-ESR before treatment of abatacept was 3.43, and that after the treatment was 1.54. Telomerase activity of CD3 positive lymphocytes decline from 0.413 to 0.156 ( $p < 0.05$ ), and that of CD19 positive lymphocytes also decline from 0.755 to 0.187 ( $p < 0.05$ ) **[conclusion]** Treatment of rheumatoid arthritis including abatacept decrease telomerase activity of CD3 positive lymphocytes and CD19 positive lymphocytes.

## P2-114

### Change of bone metabolic markers in rheumatoid arthritis patients by biologics agents using comparison analysis from Airtight study

Masahiro Tada<sup>1</sup>, Tatsuya Koike<sup>2,3</sup>, Kenji Mamoto<sup>1</sup>, Kentaro Inui<sup>1</sup>, Yuko Sugioka<sup>3</sup>, Tadashi Okano<sup>1</sup>, Hiroaki Nakamura<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Osaka City University Medical School, Osaka, Japan, <sup>2</sup>Search Institute for Bone and Arthritis Disease (SINBAD), Wakayama, Japan, <sup>3</sup>Center for Senile Degenerative Disorders (CSDD), Osaka City University Medical School, Osaka, Japan

Conflict of interest: None

**[Objectives]** It was reported that biologic agents improve bone metabolic marker (BMM) in RA. We investigated the efficacy of them for BMM by compared each drug in RA. **[Methods]** We performed prospective study (Airtight study) to investigate the effects of Abatacept (ABT) for bone metabolism. Total 165 RA patients (pts) were divided into ABT group (50 pts) and Non-ABT group (115 pts). Non-ABT group contained INF (15 pts), ETN (22 pts), ADA (38 pts), TCZ (26 pts), and GLM (14 pts). Urinary crosslinked N-telopeptide of type I collagen (NTx) and bone specific alkaline phosphatase (BAP) were used as bone resorption and formation markers. We compared change of BMM and analyzed the influenced factors by univariate analysis. **[Results]** We could gather and analyze BMM in 30 pts of ABT and 78 pts of Non-ABT. There were no significant differences about NTx and BAP in background. No significant differences was observed in NTx (ABT: -7.01, Non-ABT: -4.43,  $p=0.73$ ) and BAP (ABT: 0.44, Non-ABT: 2.21,  $p=0.33$ ). The efficacy for BMM was similar in each drug. There was negative correlation between both BMM and the change of bone mineral density in femoral neck (NTx:  $r=-0.248$ ,  $p=0.0153$ , BAP:  $r=-0.303$ ,  $p=0.0023$ ). **[Conclusion]** Each biologic agent improved BMM with no significant differences between drugs.

## P2-115

### Change of the autoantibody in effective cases by abatacept

Kensuke Oryoji, Shinichi Mizuki, Kazuo Kamada, Kenji Yoshida, Kazuhiko Higashioka, Eisuke Yokota

Division of Rheumatology, Matsuyama Red Cross Hospital, Ehime, Japan

Conflict of interest: None

**[Objectives]** To examine the change of anti-citrullinated protein antibody (ACPA) and rheumatoid factor (RF) level in patients with Rheumatoid Arthritis (RA) effectively treated by abatacept. **[Methods]** 46 RA patients administered abatacept is analyzed retrospectively. The ACPA level compared these of October-December 2012 and July-August 2014. The RF level compared these at the time of abatacept administration started and last observation. **[Results]** 22 patients continue administration of abatacept with efficacy more than 12 months. In these patients, ACPA is significantly decreased (518.4 $\pm$ 610.3 U/mL to 244.9 $\pm$ 332.7 U/mL,  $p=0.036$ ). RF is also significantly decreased (176.7 $\pm$ 222.6 U/mL to 81.3 $\pm$ 84.4 U/mL,  $p=0.011$ ), respectively. **[Conclusion]** ACPA and RF is de-

creased in patients effectively treated with abatacept. It is possible that the change of ACPA and RF correlate with clinical efficacy of abatacept in RA patients.

## P2-116

### Validation of algorithms using genome-wide SNP analysis for prediction of remission (R) or efficacy (E) for abatacept (ABT)-treated RA patients using multiple medical cohorts

Satoru Koyano<sup>1</sup>, Keiko Funahashi<sup>1</sup>, Takeshi Nakamura<sup>2</sup>, Takako Miura<sup>2</sup>, Kosuke Okuda<sup>2</sup>, Hiroaki Matsuno<sup>3</sup>, Kou Katayama<sup>4</sup>, Toyomitsu Tsuchida<sup>5</sup>, Mitsuhiro Iwahashi<sup>6</sup>, Tomomi Tsuru<sup>7</sup>, Shoichi Uchimura<sup>8</sup>, Shigeru Honjo<sup>9</sup>, Tsukasa Matsubara<sup>2</sup>

<sup>1</sup>Research Institute of Joint Diseases, Kobe, Japan, <sup>2</sup>Matsubara Mayflower Hospital, Kato, Japan, <sup>3</sup>Matsuno Clinic for Rheumatic Diseases, Toyama, Japan, <sup>4</sup>Katayama Orthopedic Rheumatology Clinic, Asahikawa, Japan, <sup>5</sup>Tsuchida Clinic, Chiba, Japan, <sup>6</sup>Higashihiroshima Memorial Hospital, Higashihiroshima, Japan, <sup>7</sup>PS Clinic, Fukuoka, Japan, <sup>8</sup>Kanzaki Municipal General Hospital, Kamikawa, Japan, <sup>9</sup>Honjo Rheumatism Clinic, Takaoka, Japan

Conflict of interest: Yes

**[Objectives]** Achievement of R or E in ABT treatment is currently one of the most important matters in RA treatment. However, there is no method for prediction of R or E. In this study, we validated the third cohort sample by using the first and second cohort algorithms. **[Methods]** The first cohort included 46 RA patients, the second, 50 patients, and the third, 40 patients, for a total of 136 patients from eight hospitals in different regions of Japan. R and E was determined by DAS28 (CRP) around 48 weeks after the initiation of treatment. We selected 10 SNPs associated with ABT-R or E which were common in both analyses of the first and second cohort ( $p < 0.05$ ). We scored the relationship between each SNP and responsiveness, the estimated total score of 10 SNPs, and then examined relationships between R (E) and non-R (non-E), and the total score in the third cohort. **[Results]** Although only 36% of the patients achieved R or E with ABT, the SNP algorithms can predict R or E with more than 60% accuracy in the third cohort samples. **[Conclusion]** These highly accurate algorithms using SNP analysis may be useful in the prediction of remission or low disease activity before treatment with ABT.

## P2-117

### Abatacept significantly reduces the serum calcium concentration

Kazuhiro Oda<sup>1</sup>, Taku Kawasaki<sup>2</sup>, Katsuhisa Kikuchi<sup>4</sup>, Noriaki Okumura<sup>1</sup>, Shinji Imai<sup>1</sup>, Yoshitaka Matsusue<sup>3</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Shiga University of Medical Science, Shiga, Japan, <sup>2</sup>Department of Rehabilitation, Shiga University of Medical Science, Shiga, Japan, <sup>3</sup>Shiga University of Medical Science, Shiga, Japan, <sup>4</sup>Department of General Surgery, Shiga University of Medical Science, Shiga, Japan

Conflict of interest: None

**[Objectives]** The new mechanism that Abatacept (ABT) directly suppresses the differentiation into osteoclasts was reported. We examined the effect on serum calcium and phosphorus concentration due to suppression of the bone resorption. **[Methods]** Rheumatoid arthritis (RA) patients were recruited ( $n=31$ ). ABT ( $n=16$ ) or TNF inhibitors (adalimumab or golimumab,  $n=15$ ) had been administered. We examined the serum calcium and phosphorus concentration at 0, 1, 3, 6 months. **[Results]** In ABT group, serum calcium concentration significantly decreased at one month and was improved to the level of pre-administration after six months. In TNF inhibitors group, it had been decreased slightly up to three months and was improved at six months. In both groups, serum phosphorus concentration was gradually reduced over the 6 months. **[Conclusion]** It has been known that the biologics suppress bone resorption by the means of inhibiting the T cell and inflammatory cytokines. We think that this conventional mechanism reduces the level of serum calcium and phosphorus concentration and that, in particular, abatacept which includes not only conventional mechanism but also new mechanism leads a strong suppression of bone resorption in early phase.

## P2-118

### Clinical evaluation of abatacept and golimumab in patients with rheumatoid arthritis in our department

Yuji Akiyama<sup>1</sup>, Yuya Yano<sup>1</sup>, Takuma Wada<sup>1</sup>, Mayuko Takamatsu<sup>1</sup>, Daisuke Ikuma<sup>1</sup>, Maiko Yanagisawa<sup>1</sup>, Yuki Shimada<sup>1</sup>, Yoshihiro Yoshida<sup>1</sup>, Noritsune Kozu<sup>1,2</sup>, Kazuhiro Yokota<sup>1</sup>, Takashi Maruyama<sup>1</sup>, Hideyuki Tachibana<sup>1</sup>, Yasufumi Shindo<sup>1</sup>, Yasuto Araki<sup>1</sup>, Hiroshi Kajiyama<sup>1</sup>, Haruhiko Akiba<sup>1</sup>, Yu Funakubo<sup>1</sup>, Kojiro Sato<sup>1</sup>, Toshihide Mimura<sup>1</sup>

<sup>1</sup>Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, <sup>2</sup>Kouzu Orthopedics Clinic

Conflict of interest: None

[Objectives] To investigate the efficacy and the adherence of abatacept (ABT) and golimumab (GLM) in RA patients. [Patients] ABT/GLM; 24 (5 males, mean 62.5 yo, mean disease duration 9.6 y)/ 23 (2 males, mean 65.8 yo, mean disease duration 10.0 y), MTX; 16 (9.25 mg/w) / 16 patients (5.3 mg/w), prednisolone; 18 (mean 5.3mg/day) / 12 patients (2.4mg/day). Bio-naïve: 6/11. [Methods] Efficacy of ABT and GLM was evaluated by DAS28-ESR4, CDAI, SDAI and HAQ for 52 weeks. [Results] 1) Mean DAS28 at the baseline (ABT/GLM): 5.88/5.766, CDAI 25.67/24.43, SDAI 28.46/28.60. The disease activity was significantly decreased in both groups. As time went by, the ratio of LDA + remission increased in both groups, respectively. No significant difference in both groups. 2) The adherence at 52 weeks showed about 80% in both groups. 3) HAQ was no difference between the base line and after the treatment in both groups, but that of Stage I+II in ABT group was significantly improved. 4) Both CRP and MMP-3 were significantly reduced in GLM group, but not in ABT group. 5) The reasons for drop-out (ABT/GLM); inadequate response 2/2, interstitial pneumonia 1/1, cough 0/1, persistent pain after injection 0/1, and erythema 0/1. [Conclusion] The efficacy and the adherence of the treatment in ABT and GLM were similar.

## P2-119

### Examination of 52 weeks of DMARDs (tacrolimus or methotrexate) used in combination with abatacept

Takayoshi Fujibayashi<sup>1</sup>, Nobunori Takahashi<sup>2</sup>, Daihei Kida<sup>3</sup>, Yuji Hirano<sup>4</sup>, Naoki Fukaya<sup>5</sup>, Toki Takemoto<sup>2</sup>, Masashi Kawasaki<sup>1</sup>, Toshiaki Okura<sup>1</sup>, Naoki Ishiguro<sup>2</sup>, Toshihisa Kojima<sup>2</sup>

<sup>1</sup>Department of Orthopedic Surgery, Konan Kosei Hospital, Konan, Japan, <sup>2</sup>Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan, <sup>3</sup>Department of Orthopedic Surgery and Rheumatology, Nagoya Medical Center, Nagoya, Japan, <sup>4</sup>Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan, <sup>5</sup>Department of Orthopedic Surgery, Kariya-Toyota General Hospital, Kariya, Japan

Conflict of interest: None

[Objective] The efficacy and safety of abatacept (ABT) on rheumatoid arthritis was evaluated by comparing patients receiving ABT plus tacrolimus (TAC group), ABT plus methotrexate (MTX group), and ABT only (non-combination group) in a multicenter study by Tsurumai Biologics Communication Registry: TBCR. [Methods] Of 383 patients who started treatment with ABT after marketing and received ABT for 52 weeks, 191 patients, excluding 6 patients who received TAC and MTX, were assigned to the TAC group (13 patients), the MTX group (66 patients), or the non-combination group (56 patients) to evaluate disease activity, retention status, and reasons for discontinuation. [Results] SDAI scores reduced from 19.8, 16.0, and 18.9 at baseline to 38.9, 21.9 and 27.2 at Week 52 in the TAC, MTX, and non-combination groups, respectively. The reduction rate was -49.1%, -26.9%, and -43.9%, respectively. There was a statistically significant difference between the TAC group and the MTX. The retention rate at Week 52 was 61.1%, 53.6%, and 49.3% in the TAC, MTX, and non-combination groups, respectively. Treatment was discontinued in 3 patients in the TAC group, none was due to adverse events. [Conclusion] A combination of ABT and TAC would appear to be as effective and safe as the ABT/MTX combination.

## P2-120

### Efficacy of Abatacept in rheumatoid arthritis patients with other collagen disease

Kazunori Yamada<sup>1,2</sup>, Kiyooki Ito<sup>2</sup>, Shigeto Horita<sup>2</sup>, Takeshi Zoshima<sup>2</sup>, Hiromi Nuka<sup>2</sup>, Satoshi Hara<sup>2</sup>, Motohiko Aizu<sup>2</sup>, Hiroshi Fujii<sup>2</sup>, Mitsuhiro Kawano<sup>2</sup>

<sup>1</sup>Department of Advanced Research in Community Medicine, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

Conflict of interest: None

[Objectives] The purpose of this study is to retrospectively evaluate the efficacy of Abatacept (ABT) in rheumatoid arthritis (RA) patients (pts) with other collagen disease (CD). [Methods] Fifteen RA pts who were treated with ABT for at least 12 weeks (wks) were enrolled. Nine pts had other CD (group A; SSc, 7; MCTD, 1; and PM, 1), and six did not (group B). The mean age was 51.9 and 59.0 years, and disease duration was 10.9 and 20.3 years, in groups A and B pts, respectively. We evaluated disease activity at 0, 12 and 24 wks after ABT therapy. We also analyzed the titer of ANA before and after the therapy. [Results] The mean DAS 28 -CRP at 0, 12, and 24 wks was 4.1, 2.9, and 2.9 in group A, and 4.2, 3.1, and 2.7 in group B, respectively. The decrease of DAS score at 24 wks was 1.5±1.1 in group A and 1.5±1.0 in group B, which was not significant. The proportion of pts achieving more than a moderate response by EULAR criteria was 75.0% in group A and 83.3% in group B. The ratio of pts who had >1:160 before ABT therapy was 77.8% in group A and 0% in group B. We evaluated 4 of 7 ANA-positive pts, and found that 3 of 4 pts had decreased ANA titer at 1-2 years after ABT therapy. The comorbid CD was not exacerbated after ABT therapy. [Conclusion] ABT was effective in RA pts with other CD.

## P2-121

### Efficacy and safety of abatacept (ABT) in patients with rheumatoid arthritis (RA) with various difficult complications to treat in our hospital

Yasufumi Kai, Shota Sakaguchi, Eiko Nishi, Hiroshi Kuroda, Toshihiko Hidaka

Institution of Rheumatology, Zenjinkai Shimin-no-Mori Hospital, Miyazaki, Japan

Conflict of interest: None

[Objectives] To investigate efficacy and safety of abatacept (ABT) in patients with RA with various difficult complications to treat in our hospital. [Methods] We examined clinical background of RA patients treated with ABT in our hospital, retrospectively evaluated its efficacy and safety. [Results] Of 29 patients (4 males, 25 females), average age at the commencement of ABT was 69.5±11.2, with RA duration 9.6 years, proportion of concomitant prednisolone 62%, DMARDs 65.5%, methotrexate 34.5%, pre-Bio (Switch) 48.3%, pretreatment DAS28-ESR 4.75±1.60, SDAI 19.6±13.5, respectively. After 12 months, DAS28-ESR, SDAI was 3.70±1.38 (p<0.01) and 10.73±11.40 (p<0.01), respectively. Overall, 3 ceased ABT for adverse event (cholecystitis, pulmonary NTM, NP-SLE), and 4 switched to other Biologics due to inefficacious of ABT by 12 months. [Conclusion] ABT is very efficacious and tolerated in patients with RA with various difficult complications to treat in our hospital.

## P2-122

### The effect and safety of combination therapy with abatacept and tacrolimus in rheumatoid arthritis patients

Shoichi Kaneshiro, Masataka Nishikawa, Yuki Etani, Hajime Owaki  
Department of Orthopaedic Surgery, Japan Community Health Care Organization Osaka Hospital, Osaka, Japan

Conflict of interest: None

Objectives: Abatacept (ABT) is a selective co-stimulation modulator of T cell activation, Tacrolimus (TAC) is also an immunomodulator that inhibits T cell activation, and we evaluated the efficacy and safety of combination therapy with ABT and TAC for RA. Method: We investi-

gated 14 patients treated with ABT who were observed over 52 weeks (Ws), and compared the efficacy and safety between ABT/MTX and ABT/TAC therapy. Results: The mean DAS28-CRP of all patients was  $4.22 \pm 1.03$  at 0, and  $2.53 \pm 0.77$  at 52 Ws after administration of ABT. The mean MMP-3 was  $235.0 \pm 109.3$  at 0, and  $67.7 \pm 36.7$  at 52 Ws. Also, the mean DAS28-CRP of 3 patients treated with ABT/TAC was  $4.96 \pm 1.37$  at 0, and  $2.90 \pm 0.75$  at 52 Ws. The mean MMP-3 was  $235.0 \pm 109.3$  at 0, and  $67.7 \pm 36.7$  at 52 Ws. Similarly, the mean DAS28-CRP of 8 patients treated with ABT/MTX was  $3.76 \pm 0.83$  at 0, and  $2.57 \pm 0.91$  at 52 Ws. The mean MMP-3 was  $179.2 \pm 69.5$  at 0, and  $66.5 \pm 32.3$  at 52 Ws. There was no significant difference between ABT/MTX and ABT/TAC in terms of the efficacy. One patient treated with ABT/TAC discontinued ABT for worsening of existing interstitial pneumonia. Conclusions: The combination of ABT and TAC is considered to be effective therapy. Careful monitoring for adverse events are necessary to obtain better benefit-risk balance of treatment with TAC

## P2-123

### Effects of abatacept in bio-naïve rheumatoid arthritis patients in clinical practice

Shuzo Yoshida, Tohru Takeuchi, Ayaka Yoshikawa, Yuko Kimura, Yumiko Wada, Koji Nagai, Shigeki Makino, Toshiaki Hanafusa  
Department of Internal Medicine (I), Osaka Medical College, Osaka, Japan

Conflict of interest: None

[Objectives] We investigated the impact of abatacept (ABA) on the bio-naïve rheumatoid arthritis (RA) patients in clinical practice. [Methods] Clinical outcome measures included the tender joint count, swollen joint count, physician global assessment of disease, patient global assessment of disease, Health assessment questionnaire disease index, erythrocyte sedimentation rate, and C-reactive protein concentration at baseline, 12, and 24 weeks. For the evaluation of disease activity, the modified Disease Activity Score using a 28-joint count-CRP (DAS28-CRP) score were used. The DAS28-CRP score was assessed at baseline, 12, and 24 weeks. [Results] The mean age was  $65.8 \pm 12.3$  years, and 89% were female. The mean disease duration was  $9.4 \pm 11.0$  years. The DAS28-CRP score decreased significantly from  $4.14 \pm 1.10$  at baseline to  $2.60 \pm 0.90$  at week 24 ( $p=0.002$ ). 33% patients were classified as showing remission. Compared with the low, mild, and high disease activity group, the remission group had a significantly lower mean DAS28-CRP score at baseline ( $3.36$  vs  $4.55$ ,  $p=0.045$ ). [Conclusion] ABA therapy resulted in clinical response in RA patients. ABA may be a useful first choice biologic regimen in bio-naïve RA patients. Lower baseline DAS28-CRP may predict achieve remission after 24 weeks.

## P2-124

### The efficacy of abatacept monotherapy in elderly patients with rheumatoid arthritis and an inadequate response to biologic disease-modifying antirheumatic drugs

Kiichiro Ando  
Tyuno Welfare Hospital, Gifu, Japan

Conflict of interest: None

[Objectives] To examine the efficacy of intravenous abatacept monotherapy in elderly patients with rheumatoid arthritis (RA) and an inadequate response to biologic disease-modifying antirheumatic drugs (DMARDs). [Methods] This study comprised three elderly patients with rheumatoid arthritis intolerant to biologic DMARDs. Patient received a 500mg intravenous abatacept therapy without methotrexate. Disease activity was assessed using the 28-joint Disease Activity Score based on the erythrocyte sedimentation rate (DAS28 ESR), the Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI). [Results] DAS28ESR (from  $3.7$  to  $2.5$ ), SDAI (from  $6.9$  to  $1.9$ ) and CDAI (from  $5.5$  to  $1.5$ ) significantly decreased from baseline to Week 24. Remission was achieved in all cases. The retention rate of abatacept at 24 weeks was 100%. No adverse event occurred. [Conclusion] These results demonstrate that abatacept monotherapy is effective in elderly patients with RA and an inadequate response to biologic DMARDs.

## P2-125

### The effects of concomitant methotrexate for incidence of large joint replacement in patients with rheumatoid arthritis treated with etanercept: A propensity score matching analysis

Shuji Asai<sup>1</sup>, Toshihisa Kojima<sup>1</sup>, Takeshi Oguchi<sup>2</sup>, Nobunori Takahashi<sup>1</sup>, Koji Funahashi<sup>1</sup>, Yutaka Yoshioka<sup>1</sup>, Toki Takemoto<sup>1</sup>, Kenya Terabe<sup>1</sup>, Nobuyuki Asai<sup>1</sup>, Naoki Ishiguro<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan, <sup>2</sup>Department of Orthopedic Surgery, Anjo Kosei Hospital, Anjo, Japan

Conflict of interest: Yes

[Objectives] To identify the effects of concomitant methotrexate (MTX) for incidence of large joint replacement in patients with rheumatoid arthritis (RA) treated with etanercept (ETN). [Methods] A retrospective cohort study was performed. 530 RA patients who received ETN were included. To reduce treatment-selection bias, propensity score matching was used. The first large joint replacement during treatment with ETN was used as the outcome variable. The cumulative incidence of large joint replacement was estimated using Kaplan-Meier curves. [Results] 120 matched pairs of patients were identified. There was good balance across most baseline characteristics except for gender. The patients with concomitant MTX tended to have a lower incidence of large joint replacement compared with those without concomitant MTX ( $P=0.263$ ). The incidence for patients with concomitant MTX hardly increased since 1 year of treatment with ETN, while the incidence for patients without concomitant MTX continued increasing. The incidence for patients with concomitant MTX was significantly lower on Kaplan-Meier estimate excluding the events occurring within the first year ( $P=0.022$ ). [Conclusion] Concomitant MTX is efficacious in retardation of incidence of large joint replacement in RA patients treated with ETN.

## P2-126

### Analyses for the change in the number of orthopedic surgery for the rheumatoid patients caused by new treatment strategy including use of biologics

Yusuke Ueda<sup>1,2</sup>, Takahiko Wada<sup>1,2</sup>, Yoshio Ozaki<sup>2</sup>, Yonsu Son<sup>2</sup>, Hirokazu Iida<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Kansai Medical University Hirakata Hospital, Osaka, Japan, <sup>2</sup>Department of Rheumatology and Clinical Immunology, Kansai Medical University Hirakata Hospital, Osaka, Japan

Conflict of interest: None

[Objectives] The changes in the treatment strategy for rheumatoid arthritis (RA) including use of biologics greatly influenced on the concept of orthopedic surgery. In current study, we evaluated the details in these changes. [Methods] From 2006 to 2013, in our institute we had performed 610 orthopedic surgeries for RA patients. In them we evaluated the change of the number of surgery between the patients had suffered RA before 2002 and ones after 2003 (the first biologics had been marketed in Japan) and the differences between the patients treated with biologics and ones without that. [Results] Of 166 surgeries performed after 2003, 12 foot and ankle surgeries had been done, while 101 of 444 had before 2002. On the other hand, of 102 surgeries performed for the patients treated with biologics, 40 foot and ankle surgeries had been done, while 73 of 501 had for ones without biologics. And 11 THAs had been performed for the patients treated with biologics, while 87 had been done for ones without biologics. [Conclusion] In newly suffered RA patients, the number of foot and ankle surgery was significantly reduced, whereas it was also considered that in the patients who had long disease duration the reduction of disease activity had facilitated to decide of receiving such surgery.

## P2-127

### Complications of joint replacement surgery in rheumatoid arthritis using biological agent

Yuki Takeda, So Nomoto  
Saiseikai Yokohamashi Tobu Hospital, Yokohama, Japan

Conflict of interest: None

**[Objectives]** We retrospectively investigated the influence of biological agents on complication after joint replacement surgery for RA. **[Methods]** Patients who underwent joint replacement surgery at our hospital. Surgery was performed 298 joint. 54 joints in patients under treatment with biological agent were collected. The mean age of these patients was 59 years and the duration of illness was 12 years. The bio group comprised 33 joints in patients treated with etanercept, 5 joints with infliximab, 2 joints with adalimumab, 2 joints with tocilizumab, 1 joint with golimumab, and 2 joints with abatacept. **[Results]** Two patients had delayed wound healing and one patient had interstitial pneumonia. There is no patient occurred infection. **[Conclusions]** Treatment with biological agents has been reported to improve the clinical symptoms of RA and delay bone destruction. But orthopedic surgery is still needed for some patients with advanced bone destruction. There have been various reports on the influence of biological agents on infection, but no consensus has been reached. Especially prosthetic joint infection can be a very serious problem. The results of our study suggest that biological agents are not risk factors for a significant increase of perioperative adverse events.

## **P2-128**

### **The trends of rheumatoid arthritis patients undergoing total hip/knee arthroplasty with biological agents**

Ken Takebe, Koji Tateishi, Hironobu Yokoyama, Yasuhiro Terashima, Natsuko Nakagawa  
Department of Orthopaedic Surgery, Konan Kakogawa Hospital, Hyogo, Japan

Conflict of interest: None

**[Objectives]** Treatment of rheumatoid arthritis (RA) has been improved remarkably in the last decade. The aim of this study is investigate the trends of patients who underwent total knee arthroplasty (TKA) with biological agents. **[Methods]** We performed 470 TKAs for RA patients from 2003 to 2013. We evaluated 58 cases which were preoperatively treated with biological agents. RA patients who underwent TKA at different periods were analyzed retrospectively. The first is 25 TKAs operated from 2003 to 2008, and the second is 33 TKAs from 2009 to 2013. Medication and preoperative disease activity in the patients who underwent TKA were investigated. **[Results]** The percentage of TKA with biological agents is getting larger. The mean age at the operation was getting older. There was no difference between two groups in the disease activity. Patients who took steroid decreased statistically, on the other hand, patients who took methotrexate (MTX) increased. **[Conclusion]** Biological agents has been shown to inhibit the progression of joint damage, however, some knees need TKA due to joint destruction even though using biological agents. Therefore, the number of TKA under biological agents is increasing. Biological agents with MTX are the current status of RA treatment.

## **P2-129**

### **Comparative evaluation of rheumatoid arthritis patients and knee osteoarthritis patients undergoing total knee arthroplasty**

Kosei Kawakami, Ryo Hiroshima, Hiromitsu Takaoka, Naoko Koenuma, Takeshi Mochizuki  
Kamagaya General Hospital, Chiba, Japan

Conflict of interest: None

**[Objectives]** We have compared the length of hospital stay (LOS), operative time, postoperative estimated blood loss, and postoperative DVT of RA patients (RA group) and OA patients (OA group) who undergoing TKA. **[Methods]** We evaluated 29 RA patients and 230 OA patients undergoing TKA at our hospital from July 2012 to August 2014. RA group were mean age 70 (62-75) years, 22 females, 7 males. OA group were mean age 75 (70-79) years, 188 females, 42 males. LOS, operative time, and postoperative estimated blood loss were compared using the Mann-Whitney U-test. Fisher's exact test was performed to test the association of the presence or absence of DVT. **[Results]** The mean LOS was 26 (19-30) days in RA group and 26 (21-33) days in OA group. The mean operative time was 72 (63-80) min in RA group and 74 (65-85) min in OA group. The mean postoperative estimated blood loss was 802 (486-1116) ml in RA group and 670 (473-886) ml in OA group. DVT positive

were 9 cases (31.0%) in RA group and 104 cases (45.2%) in OA group. There were no statistically significant differences between two groups. **[Conclusion]** There were no statistically significant differences in LOS, operative time, postoperative estimated blood loss, and the incidence of DVT between RA and OA patients undergoing TKA.

## **P2-130**

### **Long-term result of total knee arthroplasty using the FNK CR system in rheumatoid arthritis**

Gen Suzuki, Shu Saito, Takao Ishii, Masayuki Seki, Takanobu Sumino, Kunihiro Hosaka, Shinsuke Kikuta, Manabu Shimizu, Kenkou Yamada, Gouki Kinoshita, Teruyasu Oyama, Takashi Hasegawa, Yasuaki Tokuhashi  
Department of Orthopaedic Surgery, Nihon University School of Medicine, Tokyo, Japan

Conflict of interest: None

**[Purpose]** The objective of this study was to analyze the long-term results of total knee arthroplasty (TKA) using the FNK CR system in rheumatoid arthritis (RA). **[Materials and Methods]** Between September 1995 and June 2004, 185 TKAs were performed in 108 patients. Of these, 64 knees in 39 patients (6 males and 33 females) were followed up more than ten years postoperatively. The mean age at the time of TKA was 63.3 (range; 26-91) years old. The mean follow-up period was 12.5 (range; 10-18.5) years. They were evaluated clinically using the Japanese Orthopaedic Association RA knee score (JOA score), and range of motion (ROM). We also assessed radiogram and complications. **[Results]** The mean JOA score improved from 47.1 preoperatively to 82.6 at the latest follow-up. The mean range of extension improved from -8.6 degrees to -0.7 degrees. The mean range of flexion decreased from 118.6 degrees to 113.2 degrees. Three femur supracondylar fractures were identified. One case demonstrated aseptic loosening of tibial component, but no patients who required revision of implant up to the time of final follow-up. **[Conclusions]** Good clinical results were obtained with TKA using FNK CR system in RA patients over 10-year observation.

## **P2-131**

### **X-ray evaluation of PS TKA in rheumatoid arthritis**

Satomi Nagamine, Masaaki Mawatari  
Department of Orthopaedic Surgery, Faculty of Medicine, Saga University, Saga, Japan

Conflict of interest: None

**[Objectives]** RLL around tibia component of cement PS TKA in RA patients was investigated. **[Methods]** The object performed Scorpio cement PS TKA, it was 47 patients 59 knees which were possible for one year or more progress observation, and the average age was 64.8 years old at the time of operation. The average progress observation period was 38.8 months. The frequency of appearance of RLL, appearance time, zone, and the frequency of migration were investigated. **[Results]** Postoperative knee score, ROM, and the tibia component angle were good. RLL of tibia component was observed in 13/59 knee, and migration of 1 mm or more was observed in 11/59 knee. The average appearance time of RLL was 5.7 months. **[Conclusion]** Since the advance of bone resorption caused migration and loosening, it was thought that the prevention was important.

## **P2-132**

### **Optimal design of the PS-TKA with modified gap control technique**

Ryuji Nagamine, Weijia Chen  
Center of Joint Arthroplasty and Rheumatism, Fukuoka Tokushukai Medical Center, Fukuoka, Japan

Conflict of interest: Yes

**[Objectives]** Optimal design of PS-TKA was assessed. **[Methods]** Component size, rotation angle of the femoral component, patella position in the sagittal plane, usefulness of the reduction osteotomy of the tibia were assessed in PS-TKA cases. 3D finite element model analysis was also done to evaluate the equivalent stress of the post-cam mechanism

and tibial articular surface. Effect of mal-rotated tibial component on equivalent stress of the tibial post and tibial articular surface was also assessed. With these data, optimal design of the PS-TKA with modified gap control technique was discussed. [Results] The results showed that AP/ML ratio and design of the patellar groove should be modified because PCL resection enlarges the joint gap in flexion and rotation angle of the femoral component varies. Round tibial post and single radius design are necessary to minimize contact stress. Reduction osteotomy of the tibia is useful in varus knees and no problem occurs with this technique. Operative techniques such as proper rotational alignment of the tibial component are also important even with good design in order to obtain optimal clinical results with PS-TKA. [Conclusion] Optimal design should be different between CR and PS.

### **P2-133**

#### **Disease activity of rheumatoid arthritis and the administration of a drug before and after total knee arthroplasty**

Taro Tezuka, Ken Kumagai, Yutaka Inaba, Kengo Harigane, Yoshihiro Kusayama, Akiko Nagaoka, Tomoyuki Saito  
Department of Orthopedic Surgery, Yokohama City University, Yokohama, Japan

Conflict of interest: None

[Objectives] The present study aimed to investigate the disease activity of rheumatoid arthritis in patients who underwent total knee arthroplasty (TKA). [Methods] The study included 28 knees of 28 patients who underwent TKA between 2007 and 2012, and were followed for at least 2 years. The mean age of the patients at TKA was 66.8 years. Of the 28 knees, 4 were classified as Larsen grade III, 15 as grade IV, and 9 as grade V. DAS 28 was calculated before and after TKA. Additionally, we investigated the administration of a drug before and after TKA. [Results] The mean DAS 28 score was  $4.3 \pm 1.0$  points before TKA and significantly improved to  $2.9 \pm 0.8$  points 1 year after TKA. Before TKA, 16 patients were treated with methotrexate (MTX) and no patients was newly treated with MTX. The mean amount of MTX was  $6.7 \pm 4.3$  mg/week preoperatively, and  $7.9 \pm 4.1$  mg/week postoperatively (N.S.). Two patients were treated with Infliximab, 2 with etanercept, and 1 with tocilizumab. After TKA, 2 patients were treated with etanercept and adalimumab. [Conclusion] The findings of this study indicate the effect of TKA on disease activity of rheumatoid arthritis.

### **P2-134**

#### **Total knee arthroplasty for rheumatoid arthritis after unicompartmental arthroplasty: A case report**

Kazue Hayakawa, Hideki Date, Sho Nojiri, Takuya Funahashi, Harumoto Yamada  
Department of Orthopaedic Surgery, Fujita Health University School of Medicine, Aichi, Japan

Conflict of interest: None

[Objectives] We report a patient who underwent total knee arthroplasty (TKA) due to the development of rheumatoid arthritis (RA) after unicompartmental knee arthroplasty (UKA). [Patient] A 72-year-old woman had undergone medial left knee UKA 8 years earlier at another hospital. She presented with left knee pain for 8 months that had not responded to conservative therapy, and visited our Department for surgical assessment. Plain X-ray films showed no radiolucent lines around the prosthesis, but cartilage destruction was noted at the lateral condylar regions of the femur and tibia. Laboratory tests revealed that anti-CCP antibodies were 190.3 U/mL, MMP3 was 732.2 ng/mL, RF was 101 U/mL, CRP was 3.6 mg/dL, and the erythrocyte sedimentation rate was 129 mm/h. For surgery, we used a NexGen CR Flex Reactive changes suggesting active RA were detected by histological examination of the resected synovium. Bone scintigraphy and gallium scintigraphy were performed after the surgery, but no active lesions were observed at other sites. [Discussion] UKA is a less invasive surgical approach that has many advantages, and favorable long-term results have been reported. We consider that it is necessary to follow-up patients after such surgery while keeping the possible development of RA in mind.

### **P2-135**

#### **A case of simultaneous knee arthroplasty in seronegative RA of severe varus knees**

Shoichi Taniguchi, Hiroki Watanabe  
Hachiya Orthopaedic Hospital

Conflict of interest: None

In elderly patients with knee pain severe deformity such as varus deformity is often accompanied by rheumatoid arthritis. case presentation: We present a patient with simultaneous bilateral varus and patellofemoral OA of the knees that equally contributed to overall disability. This 72 years old, motivated and otherwise healthy patient presented to our hospital with his upper arm and bilateral knee pain. There were severe contracture of knee,  $195^\circ$  of femoral tibia angle (FTA) and moderate defect of medila proximal tibia with X-ray findings. Laboratory finding shows 9.3 of CRP and 1009 of MMP-3 without positive finding of RF and anti CCP antigen. He was treated by simultaneous bilateral total knee arthroplasty without allograft and was allowed to gait with full weight bearing using knee brace and was able to gait with T-cane a few weeks after postoperatively. Outcome showed excellent alignment and function of replaced joints. However, he was requested to take DMARDs and MTX 3-6 weeks postoperatively due to recurrent swelling of multiple joint. conclusion: Simultaneous knee arthroplasty in seronegative RA of bilateral deformed knees resulted in a better functional outcome However, we should be aware of careful preoperative planning, a timing of surgical indication.

### **P2-136**

#### **Short-term clinical and radiographic results of total hip arthroplasty for patients with rheumatoid arthritis**

Shuichi Miyamoto, Junichi Nakamura, Masahiko Suzuki, Shigeo Hagiwara, Takanori Omae  
Dept. of Orthop. Surg, Graduate School of Medicine, Chiba University, Chiba, Japan

Conflict of interest: None

[Objectives] The good clinical results of total hip arthroplasty for patients with rheumatoid arthritis were reported. In this study, we reported for a short term clinical results and radiographic findings of THA in RA patients. [Methods] From January 2003 to September 2014, we evaluated 18 THA. Follow-up rate of all patients with RA was 89.7%. Patients who had hip diseases were 10.2%, and in them THA was performed 51%. The mean age at surgery was 62.4 years and the mean follow-up period was 38.9 months. Clinical results were evaluated by JOA score. Complications were investigated. Radiographic examinations were performed. [Results] The mean JOA hip score improved from 32.7 points to 72.4 points. As complication, 1 infection, 2 intraoperative fracture occurred. Dislocations were none. Stress shielding was grade 1 in 6 hips, grade 2 in 5 hips and grade 3 in 1 hips. No hips were grade 4. Cortical hypertrophy was 1 hips. Pedestal sign was 5 hips. Subsidence was 0.38mm in uncemented group and 0.52mm in cemented group. As for cementing grade, grade A was in 5 hips, grade B in 1 hips. No hips were grade C1, C2 and D. Acetabular cup was stable was in 9 hips, possibly unstable was in 8 hips. [Conclusion] In our study, the short-term clinical and radiographic results of THA were satisfactory.

### **P2-137**

#### **Short term result of the cementless THA with the bone graft for rheumatoid arthritis patient**

Kazuo Fujiwara<sup>1</sup>, Yosuke Fujii<sup>2</sup>, Keiichiro Nishida<sup>2</sup>, Toshifumi Ozaki<sup>2</sup>  
<sup>1</sup>Department of Intelligent Orthopaedic System Development, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan, <sup>2</sup>Department of Orthopaedic Surgery Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

Conflict of interest: None

[Objectives] We performed cementless total hip arthroplasty (THA) with autologous bone graft for rheumatoid arthritis (RA) patient. We re-



ported the short term result of cementless THA for RA patient. [Methods] We treated 18 hips in 15 patients (3 males and 12 females) by cementless THA. Implants were AMS HA cups and PerFix stems (Kyocera Medical, Osaka) and Trident HA cups and Accolade stems (Stryker, Tokyo). We evaluated the stability of implants according to the CT image and X-ray. We calculated JOA score and investigated complications during operation and after operation. [Results] There was no loosening at the cup and no complication after operation. The graft bone engaged to acetabular fossa in all cases. [Conclusion] It was useful method for recover the bone stock of acetabular fossa to impact the autologous bone graft for RA patient.

## P2-138

### Short term result of cementless acetabular fixation without screws in rheumatoid arthritis patients

Yoshio Uchida, Takuji Nishikawa, Hiroshi Takahashi, Yuichi Nagase, Kenichi Shimane  
Tokyo Metropolitan Bokutoh Hospital Tokyo, Japan

Conflict of interest: None

[Objectives] We compared initial stability and clinical results of finned cementless acetabular components with and without screws fixation. [Methods] Among 75 first total hip prosthesis joints which we carried out in our hospital by January, 2014 from November, 2006, We intended for 36 joints which performed Mallory Head Finned cup (Biomet) for rheumatoid arthritis patients. The radiographic evaluation compared the last observation with the operated day and observed the change of the appearance angle, presence of osteolysis, migration, and initial gap. [Result] Female 32 joint, male 4 joint. non hole (screw non-use), multi hole (screw used) were 18 joint, respectively. The average age is non hole 69.5 (55-83), multi hole 66.0 (54-87), respectively. The average followup period was non hole 16.8 months, multi hole 36.2 months. Although loosening at X ray assessment was re-replacement there one case in multi hole, other elements did not differ between two groups. Postoperative dislocation, fracture non hole, multi hole there one by each one cases, infection was not in either. [Conclusion] The initial fixation of the finned cementless acetabular cup without screws in rheumatoid arthritis patients was very good. And the obvious problem during an observation period was not seen.

## P2-139

### Combination therapy of denosumab and teriparatide for the glucocorticoid induced osteoporosis in RA

Sumito Kawamura<sup>1</sup>, Michio Minami<sup>2</sup>  
<sup>1</sup>Department of Orthopaedic Surgery, Kobayashi Hospital, <sup>2</sup>Department of Orthopaedic Surgery, Hokkaido Orthopaedic Memorial Hospital

Conflict of interest: None

[Objectives] The guideline for the treatment of glucocorticoid-induced osteoporosis (GIOP) was published. There was a report of combination therapy of teriparatide and denosumab for the postmenopausal osteoporosis. We report the clinical result of combination therapy of denosumab and teriparatide for the GIOP among RA patients. [Methods] There were ten RA patients diagnosed as GIOP in our department. They were given both denosumab and teriparatide. The average dosage of glucocorticoid was 3.5mg/day. The bone mineral density (BMD) of lumbar spine and femoral neck were measured at 3, 6, and 12 months from the first. The bone markers (TRACP-5b and PINP) and the health-related QOL status (EQ-5D) were examined. [Results] The lumbar spine BMD was significantly improved 24.3% at 12 months compared with the baseline and also the femoral neck BMD was improved 45.3% as well. TRACP-5b was gradually decreased from the beginning and PINP was started to decrease from 6 months following the first. EQ-5D was also improved compared with the baseline. [Conclusion] The clinical result of combination therapy of denosumab and teriparatide for the GIOP among RA patients was exciting in the BMD. The difference among serological markers may explain the "anabolic window" effect in this study.

## P2-140

### The effectiveness of denosumab (DMAB) in patients with glucocorticoid induced osteoporosis (GIO)

Mari Ushikubo<sup>1</sup>, Ikuko Tanaka<sup>2</sup>, Harumi Kuda<sup>1</sup>, Keisuke Izumi<sup>1</sup>, Shigenori Tamaki<sup>2</sup>, Kumiko Akiya<sup>1</sup>, Hisaji Oshima<sup>1</sup>

<sup>1</sup>The Department of Connective Tissue Disease, National Tokyo Medical Center, <sup>2</sup>Nagoya Rheumatology Clinic

Conflict of interest: None

[Objectives] To clarify the effectiveness of DMAB in patients with GIO. [Methods] Patients with connective tissue disease (n=26) were included and use DMAB. We evaluate the bone turn over markers (BMT), bone mineral density and incident fracture every 6 months. [Results] 1) The mean age, disease duration, the glucocorticoid dosage at the base line, the number of patients who had prevalent fracture were 66±11 years old, 14±11 years, 8±6 mg/day (prednisolone equivalent), 17 patients, respectively. The number of patients whose pre-treatment before DMAB use were bisphosphonate 11, teriparatide 7 and none 8. 2) The mean level of TRACP-5b, PINP and ucOC at the baseline were 352±230 mg/dl, 55.7±65.9 µg/L, 3.84±5.63 ng/ml, respectively. The level of BMTs decreased and Changes from baseline for them were significant at 6<sup>th</sup> months. 3) The mean level of BMD at the lumbar spine and neck at the baseline were 76±14%, 74±13%, respectively. At 6 month, Lumbar spine and the neck BMD increased 4% and 3.1% relative to baseline. 4) one incident fracture were seen during first 6 months. 5) No clinical hypocalcemia were seen. [Conclusion] DMAB would be effective in GIO.

## P2-141

### Efficacy of Denosumab among steroid treated rheumatoid patients

Koyu Hoshino, Ayako Fujimoto, Komei Sakata, Eiko Miyagawa, Mikako Iwakura, Shinya Hirata  
Department of Hematology and Rheumatology, Kumamoto University School of Medicine, Kumamoto, Japan

Conflict of interest: None

[Objectives] The steroid therapy is a main treatment for rheumatoid disease while it has an adverse effect such as osteoporosis. Recently, Denosumab was approved to osteoporosis treatment. Therefore, we estimated the efficacy of Denosumab among steroid treated patients. [Methods] Efficacy of Denosumab was estimated using dual-energy X-ray absorptiometry (DEXA) method in 11 steroid treated patients. [Results] Mean of DEXA value was increased 0.081g/cm<sup>2</sup> per year in this cohort. [Conclusion] Denosumab for steroid treated patients was effective. Efficacy of Denosumab appeared comparatively rapid. This result indicates that administration of Denosumab from early phase is suitable for steroid treated rheumatoid disease patients.

## P2-142

### Effect of switching from bisphosphonates to denosumab on the bone mineral density and quality of life (QOL) in patients with connective tissue disease treated with adrenocorticosteroid

Yasuaki Nagare<sup>1</sup>, Tetsu Itami<sup>1</sup>, Kenji Sakai<sup>1</sup>, Asuka Inoue<sup>1</sup>, Chiemi Tasaki<sup>1</sup>, Shinkai Ri<sup>1</sup>, Taeko Yumoto<sup>2</sup>, Kayo Asato<sup>1</sup>, Toshihiko Shiga<sup>1</sup>, Shoichi Hino<sup>1</sup>, Tomohiro Yano<sup>1</sup>, Kazuya Kishimoto<sup>1</sup>, Hideki Shimazu<sup>2</sup>, Yuji Nozaki<sup>1</sup>, Koji Kinoshita<sup>2</sup>, Masanori Funachi<sup>1</sup>, Itaru Matsumura<sup>1</sup>

<sup>1</sup>Department of Hematology and Rheumatology, Kinki University Faculty of Medicine, <sup>2</sup>Department of Rheumatology, Sakai Hospital Kinki University Faculty of Medicine

Conflict of interest: None

[Purpose] Adherence rate with medication using oral bisphosphonates (BP) are not necessarily high, because of the complication derived from oral administration. At present, there have been few reports investigating satisfaction and adherence with medication of BP in the patients with connective tissue disease. We investigated whether denosumab (DMAB) improved the bone mineral density and QOL after switching from BP to DMAB. [Method] From July 2013 to October 2014, we evaluated 35 patients whose medication was switched to DMAB from oral BP and observed for more than six months. We conducted a ques-

tionnaire survey about the patient's adherence with the medication using oral BP and the merit or demerit of switching. After six months, we measured the bone mineral density of the femur and lumbar spine. **[Results]** 31/35 patients (89%) could continue taking BP. However, 21/35 patients (60%) felt difficulty taking BP orally. After switching to DMAB, satisfaction with medication was greatly improved. Six months after switching, the rate of change in the bone mineral density in the lumbar spine and femur was  $4.95 \pm 8.53\%$  and  $1.30 \pm 5.88\%$  respectively. **[Conclusion]** These results suggest that switching from BP to DMAB improved satisfaction levels and the QOL of the patients.

### P2-143

#### Ineffective fracture prevention by bisphosphonate in patients undergoing high dose glucocorticoid therapy

Goichi Kageyama<sup>1</sup>, Takaichi Okano<sup>1</sup>, Yuzuru Yamamoto<sup>1</sup>, Daisuke Sugiyama<sup>2</sup>, Goh Tsuji<sup>3</sup>, Shunichi Kumagai<sup>3</sup>, Akira Onishi<sup>1</sup>, Yoshinori Kogata<sup>1</sup>, Jun Saegusa<sup>1</sup>, Akio Morinobu<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Kobe University Hospital, <sup>2</sup>Keio University, <sup>3</sup>Shinko Hospital

Conflict of interest: None

**[Objectives]** High dose glucocorticoid (GC) therapy (PSL > 0.8 mg/kg/day) is often provided to patients with systemic rheumatic disease. Although bisphosphonate (Bis) is frequently used as a first-line prevention of GC induced osteoporosis (GIO), there is limited data about the effect on the prevention of fragility fracture with the patients undergoing high dose GC. Our aims are the evaluation the effect of fracture prevention by Bis in the patients with high dose GC therapy. **[Methods]** We conducted a retrospective study. We included the rheumatic disease patients who are treated with PSL > 0.8 mg/kg/day and postmenopausal women or men > 40 years old. Primary Outcome is major osteoporotic fracture after high dose GC therapy **[Results]** 131 patients are included. Mean observation period is 1558 days. 51 patients suffered from fragility fractures. Furthermore, 32 patients got fractures despite taking Bis. Kaplan-Meier analysis revealed that Bis had no effect in reducing fractures in patients with high dose GC therapy. Multivariable analysis also showed that Bis taking did not reduce the fragility fractures, FRAX and two or more times high dose GC therapy was associated with fractures **[Conclusion]** Bis have insufficient effect of fractures prevention in patients undergoing high dose GC therapy.

### P2-144

#### Efficacy and safety of osteoporotic treatment with eldelcalcitol in rheumatic disease patients

Fuminori Hirano

Department of Internal Medicine, Asahikawa Medical Center, Asahikawa, Japan

Conflict of interest: None

**[Objectives]** The aim of this study is to evaluate the efficacy and safety of osteoporotic treatment with eldelcalcitol in rheumatic disease patients. **[Methods]** Eldecalcitol was daily administered to 43 rheumatic disease patients at a dose of 75 µg for 24 months. Lumbar and total hip bone mineral density were measured at 0, 6, 12 and 24 month. Serum Ca, P, TRACP-5b, bone-specific AP (BAP), P1NP, parathyroid hormone (PTH) and urinary type-I collagen cross-linked-N-telopeptide (uNTx) were measured. **[Results]** The percentage changes from baseline (0 month) in lumbar and total hip bone mineral density were increased in eldelcalcitol alone group (n=19) and eldelcalcitol plus bisphosphonate group (n=17) at 6, 12 and 24 month. In addition, Serum Ca was significantly increased at 6 month and TRACP-5b, uNTx, P1NP and BAP were significantly decreased at 6 month as compared to each biomarker at baseline. In contrast, hypercalcemia was found in 7 patients who have renal dysfunction (CKD category; under G3a, eGFR < 60). **[Conclusions]** Eldecalcitol was effective in osteoporotic treatment in rheumatic disease patients. Especially, eldelcalcitol was also useful for bisphosphonate-resistant osteoporotic treatments. In contrast, hypercalcemia was adverse effects in patients with renal dysfunction.

### P2-145

#### The effect of bone turnover markers in patients with rheumatoid arthritis taking Abatacept

Daihei Kida<sup>1</sup>, Nobunori Takahashi<sup>2</sup>, Yosuke Hattori<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery and Rheumatology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan, <sup>2</sup>Department of Orthopedic Surgery and Rheumatology, Nagoya University School of Medicine, Nagoya, Japan

Conflict of interest: Yes

**[Objectives]** The aim of this study was to confirm the effects of Abatacept (ABT) on bone formation and resorption. **[Methods]** Fourty-four Japanese rheumatoid arthritis (RA) patients (mean age 68.4, 10 male and 34 female) were enrolled in this study. These patients were treated with ABT once a month since Oct. 2010. Bone metabolic markers were measured at baseline and at 12 months. **[Results]** At 12 months of ABT treatment, DAS28ESR (4) and mHAQ were improved significantly from baseline. There was an increase of serum bone-specific alkaline phosphatase (BAP) in patients who had received ABT at 12 months, compared to the baseline:  $33.7 \pm 14.7$  vs.  $39.0 \pm 18.6$  (microg/L). The urine cross-linked N-telopeptides of type I collagen (NTx) activity of ABT treatment was also changed at 12 months compared to the baseline:  $51.0 \pm 26.4$  vs.  $48.0 \pm 23.8$  (nmolBCE/). **[Conclusion]** These results showed that ABT treatment were up regulated bone formation and down regulated bone resorption. Consequently, ABT seems likely to return toward normalization of bone turnover in RA patients.

### P2-146

#### A case of the inflammatory OA successfully treated with Tocilizumab

Masahiro Kondo, Mayuko Moriyama, Yoshiko Sumita, Yohko Murakawa  
Department of Rheumatology, Faculty of Medicine, Shimane University

Conflict of interest: None

**[Case]** 81 years old woman **[Chief complaint]** Polyarthralgia **[Present illness]** The patient was diagnosed as PMR at 2009 and medicated with PSL. The arthralgia with the rise of CRP and MMP-3 develops in 2013. After that, she presented both swelling and pain of the wrist and PIP joints, although both RF and anti-CCP antibody were negative. She was diagnosed as RA and started the treatment with SASP but cancelled since drug rash was appeared. The effects of bucillamine, tacrolimus, or golimumab, were insufficient. So she was consulted to our hospital in July 2014. The joint of the bilateral PIP, DIP, wrist and knee were swollen and tender remarkably. She had CRP 8.6 mg/dl and MMP-3 565.9 ng/ml and high disease activity. In the plain X-ray, gull-wing deformity was observed in the bilateral PIP and DIP joints, and it showed the evidence which suggests IOA rather than RA. The joint destruction was progressed rapidly during six months. Therefore after the treatment with tocilizumab, joint swelling and tenderness were gradually improved. **[Discussion]** The potency of TNF inhibitor or IL-1 inhibitor has been reported recently. Tocilizumab, but not golimumab showed the favorable effect on this patient. To our knowledge, this is the first report of the validity of tocilizumab against IOA.

### P2-147

#### Mycophenolate mofetil in the treatment of lupus cerebrovascular disease

Kazuhiko Higashioka, Kenji Yoshida, Kensuke Oryoji, Kazuo Kamada, Shinichi Mizuki, Eisuke Yokota

Division of Rheumatology, Matsuyama Red Cross Hospital, Ehime, Japan

Conflict of interest: None

We report a case of neuropsychiatric systemic lupus erythematosus (NPSLE) successfully treated with mycophenolate mofetil (MMF). The patient was a 40-year-old female with a past history of lupus nephritis (type V) that resolved completely with long-term oral cyclophosphamide treatment (total about 43 g) and subsequent observation on prednisolone 7mg/day plus azathioprine 100mg/day. Transient ischemic attack (TIA), which showed dysarthria, weakness in the upper and lower extremities

and numbness in the right upper and lower extremities occurred repeatedly despite administration of these medicines. RCVS was proved by taking MRI twice, but RCVS didn't sufficiently explain all symptoms and a high level of IL-6 in spinal fluid was recognized: therefore the diagnosis of NPSLE was made. Initially prednisolone was increased to 20mg/day and azathioprine was increased to 150mg/day, but the symptoms persisted. MMF was chosen as the next therapy and the symptoms resolved completely. In addition, the high level of IL-6 in spinal fluid decreased significantly. MMF apparently was effective for this patient. To our knowledge, this is one of a few reported cases of effective treatment by MMF of NPSLE. It may be suggested that MMF is effective for NPSLE

## P2-148

### **Influence of renal complication on efficacy and adverse event of tacrolimus combination therapy in patients with systemic lupus erythematosus (SLE) under maintenance phase - nested case-control study-**

Yusuke Miwa, Kumiko Otsuka, Airi Nishimi, Shinichiro Nishimi, Shinya Seki, Sho Ishii, Yoko Miura, Nao Oguro, Takahiro Tokunaga, Ryo Takahashi, Tsuyoshi Kasama

Division of Rheumatology, Department of Medicine, Showa University School of Medicine

Conflict of interest: Yes

[Objectives] The purpose of the study was to investigate whether renal complication affects efficacy and safety of the tacrolimus combination therapy in SLE patients under maintenance phase. [Methods] Fifty-seven SLE patients (A: 30 cases with renal complication, B: 27 cases without) were included. Presence of renal complication was defined as proteinuria  $\geq 0.5$ g/d and lupus nephritis by renal biopsy. Major outcome measures include SLEDAI, steroid dosage, proteinuria, serum anti-dsDNA Ab, C3 and Cr level and eGFR. The patient's background factors include age, gender, disease duration, ACE-I/ARB and statin therapies. We compared these outcome measures between pre-treatment and one year after. [Results] SLEDAI was improved in both groups ( $7.2 \pm 5.0$  to  $2.8 \pm 2.3$  in A,  $6.4 \pm 3.8$  to  $2.4 \pm 2.2$  in B,  $p < 0.001$ ), serum C3 level was improved ( $65.9 \pm 24.6$  to  $77.7 \pm 18.2$  mg/dl in A, and  $81.8 \pm 23.0$  to  $90.6 \pm 19.4$  mg/dl in B,  $p = 0.0021$ ; between pre- and post-treatment). Anti-dsDNA antibody level was reduced, and serum Cr and eGFR levels were slightly exacerbated. No cases developed end-stage renal failure requiring artificial dialysis. [Conclusion] Tacrolimus combination therapy has additive beneficial effects on reduced proteinuria and increased serum C3 level in SLE patients with renal complication under maintenance phase.

## P2-149

### **Efficacy of tacrolimus for maintenance therapy in patients with active lupus nephritis**

Shinji Morimoto<sup>1</sup>, Takuya Hirai<sup>1</sup>, Kana Tanji<sup>1</sup>, Keigo Ikeda<sup>1</sup>, Yoshinari Takasaki<sup>2</sup>, Iwao Sekigawa<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Juntendo University Urayasu Hospital, <sup>2</sup>Department of Internal Medicine and Rheumatology, Jutendo University School of Medicine

Conflict of interest: None

[Objectives] To evaluate efficacy of tacrolimus (Tac) for maintenance therapy with active lupus nephritis (LN). [Methods] We subjected the cases at our hospital as we diagnosed LN, and used Tac for the maintenance treatment. We analyzed the clinical information retrospectively such as WHO pathological tissue classification, treatment, and outcome. [Results] Tac was administered for 45 cases of maintenance therapy phase of lupus patients. Renal biopsy was performed at 24 cases, these were type II (5 cases), type III (1 case), type IV (14 cases), type V (2 cases), and type IV+V (2 cases). Traf level of Tac was 4.9 ng/ml (mean). Remission rate was 85.3% and above all of first nephritis cases were complete remission state. We did not recognize chronic kidney failure and artificial dialysis. [Conclusion] We consider that Tac is effective for maintenance therapy with active LN.

## P2-150

### **A case of systemic lupus erythematosus with various manifestations including choroidal detachment associated with the change of auto-antibody profile**

Rina Furukusa, Tomoya Harada, Yuko Okamoto, Masanori Hanaoka, Daisuke Hoshi, Tsuyoshi Kobashigawa, Hisae Ichida, Yasuhiro Katsumata, Yasushi Kawaguchi, Atsuo Taniguchi, Hisashi Yamanaka  
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Case] A woman in her 50s visited our clinic 20 years ago because of Raynaud's phenomenon and arthritis. Anti-U1-RNP antibody was detected but she did not have major organ damage. Thus, she was followed without medication. Several years ago, anti-Sm, anti-dsDNA, and anti-Ro/SS-A antibodies were converted to positive. She had blepharidema 15 days ago and subsequently got influenza. Then, because muscae volitantes, abdominal bloating, and weight gain developed, she was emergently hospitalized. Generalized edema and thoracoabdominal fluid collection were caused by hypoalbuminemia, which was derived from lupus nephritis and proteinlosing gastroenteropathy. In addition, choroidal detachment secondary to choroiditis resulted in severe visual field defect. We diagnosed them as symptoms of SLE, and they were successfully treated with high-dose steroids, intravenous cyclophosphamide, and plasmapheresis. [Clinical Significance] Chorooidopathy is a rare ocular manifestation of SLE, and choroidal detachment due to SLE was reported in only two cases. This case report demonstrated that 1) Various manifestations of SLE can develop in a quiescent patient with a change of autoantibody profile; 2) Choroidal detachment can occur secondary to choroiditis when the colloid osmotic pressure decreased.

## P2-151

### **Successful treatment of thrombotic thrombocytopenic purpura associated with systemic lupus erythematosus with early administration of rituximab**

Naoya Nishimura, Naoyasu Ueda, Tsuyoshi Kawaguchi, Akira Ueda  
Department of Rheumatology and Infectious Diseases, Miyazaki Prefectural Miyazaki Hospital, Miyazaki, Japan

Conflict of interest: None

A 44-year-old female with a 19-year history of systemic lupus erythematosus (SLE) was admitted to our hospital due to fever, fatigue and purpura on extremities lasting for a week. Laboratory tests revealed anemia (Hb 6.2 g/dL), thrombocytopenia (Plt 17,000/ $\mu$ L) and LDH 912 IU/L. High-dose glucocorticoid and intravenous immunoglobulin were started. Since additional laboratory tests showed undetectable level of ADAMTS13 activity and positivity for ADAMTS13 inhibitor (6.6 BU/mL), we diagnosed thrombotic thrombocytopenic purpura (TTP) and started plasma exchange (PE) and weekly rituximab (RTX) infusion (375mg/m<sup>2</sup>) on hospital day 5. Inhibitor decreased to 0.7 BU/mL on day 8 but increased again to 3.1 BU/mL on day 13 and decreased again to 0.9 BU/mL on day 19. Her clinical and laboratory abnormalities were resolved and PE ceased on day 17. Weekly rituximab were performed a total of 8 times. Some TTP cases exhibit ADAMTS13 inhibitor boosting after PE. They are refractory to high-dose glucocorticoid and PE but have good response to RTX. In our case with reascent of inhibitor, early administration of RTX was effective.

## P2-152

### **Influence to give to curative effect and a side effect of a tacrolimus dose and the blood concentration for systemic lupus erythematosus**

Youhei Fujiki, Takuya Kotani, Reiko Wakura, Yumiko Wada, Shuzo Yoshida, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa  
First Department of Internal Medicine, Osaka Medical College, Takatsuki, Osaka, Japan

Conflict of interest: None

[Objectives] To assess the influence that a dose and blood concentration of tacrolimus (Tac) give to curative effect and a side effect for SLE

retrospectively. [Methods] 25 patients were treated with prednisolone and Tac, but not with other immunosuppressant. Observation period was six months after tacrolimus start. [Results] Regarding patient background, 20 patients were female, and the median values were as follows: age, 43 years (15-69); C3 at pretreatment, 54 mg/dl (27-139); anti-ds-DNA antibody, 46.2 IU/ml (0-7012); SLEDAI-2K, 14 (4-45); initial dosage of prednisolone, 52.5 mg/day (10-90); Tac dosage, 3 mg/day (1-5); and Tac trough level, 4.5 ng/ml (1.3-8.5) Tacrolimus dose and the blood concentration correlated with improvement of the number of the platelets, C3, the titer of anti-dsDNA-Ab and SLEDAI-2K, particularly in a group with more than of dose 3.5mg/day of Tac ( $P=0.01, 0.05, 0.01, 0.04$ ) In the group with blood concentration of Tac more than 5ng/ml, number of the platelets, C3, the titer of anti-ds-DNA-Ab were significantly improved. ( $P = 0.04, 0.01, 0.001$ ) The blood concentration and the dose of Tac were not related to the onset of side effect. [Conclusion] The possibility that a high dose Tac and trough level >5ng/ml were useful was suggested.

## P2-153

### The measurement of anti aquaporin-4 (AQP4) antibody was useful for diagnosis in a case of the neuromyelitis optica associated diseases (NMOSD) with systemic lupus erythematosus (SLE)

Okinori Murata, Nobuhito Sasaki, Yuka Oikawa, Ami Matsumoto, Kouko Kowata, Yukari Ninomiya, Hitoshi Kobayashi, Kohei Yamauchi  
Internal Medicine, Department of Respiratory, Allergy, Rheumatology, Iwate Medical University School of Medicine, Iwate, Japan

Conflict of interest: None

Myelitis and optic neuritis are reported to occur in SLE, whereas the case with NMOSD is complicated with SLE. In addition, it was reported that both occurred at the same time. A 37-year-old woman presented with intractable hiccups, feeling of photophobia, diplopia, dysphagia and dysesthesia of the face. A spinal Magnetic resonance imaging (MRI) showed a high intensity lesion from medulla oblongata to C2 on the T2-weighted images. Anti AQP4 antibody was positive in cerebrospinal fluid. Therefore she was diagnosed NMOSD. She was also diagnosed SLE based on the following findings: butterfly rash, discoid eruption, positive anti-double-stranded DNA antibodies and positive antinuclear antibody. The treatment was started with pulse therapy of methylprednisolone followed by oral prednisolone 60mg/day in combination with azathioprine, intravenous immunoglobulin and 4 times of immune adsorption therapy. After these treatments, the clinical symptoms were markedly improved. Afterwards, no relapse was observed. There has been no evidence that cyclophosphamide is effective for NMOSD. When a patient with SLE is suspect of the complication with NMOSD, the measurement of anti AQP4 antibody was thought to be important for differential diagnosis with neuropsychiatric SLE.

## P2-154

### A case of thrombotic thrombocytopenic purpura (TTP) in systemic lupus erythematosus (SLE), who had exacerbated by infection of influenza A, and was successfully treated with rituximab

Shuko Hashimoto, Teruhisa Azuma, Hiroyasu Ishimaru, Kazuhiro Hatta  
Department of General Internal Medicine, Tenri Hospital, Nara, Japan

Conflict of interest: None

[Case] A 39-year-old female of SLE was been to our hospital. She has been in low SLE activity with no medication for 9 years. She noticed urine color change, purpura on her body, and progressive dyspnea of exertion before admission. Laboratory tests was thrombocytopenia and hemolytic anemia with a low level of ADAMTS13 activity and a high anti-ADAMTS13 inhibitor level, showing TTP. We started high-dose methylprednisolone and plasma exchange. The platelet increased on the 4th day. However the next day she was infected with influenza A virus, the platelet decreased again. Abdominal pain and coma was appeared, treatment of prednisolone and plasma exchange apparently didn't response anymore, so rituximab was administered. The platelet recovered on 15th day, and anti-ADAMTS13 inhibitor was loss 5 days later. Her conditions fully recovered. [Conclusion] TTP is rare complication in SLE, it isn't associated with SLE activity, and influenza A triggers TTP. Treatment isn't established yet, but plasma exchange is the first choice to

remove anti-ADAMTS13 inhibitor, and also recommends to administer rituximab in case of relapse or refractory TTP. Clinical importance of this case is that TTP with low SLE activity was progressed by infection, and was successfully treated with rituximab.

## P2-155

### Long myelitis in systematic lupus erythematosus; a case report

Takanori Ichikawa<sup>1</sup>, Naoki Ezawa<sup>1</sup>, Kenichi Hoshi<sup>1</sup>, Hiroyuki Yahikozawa<sup>1</sup>, Dai Kishida<sup>2</sup>

<sup>1</sup>Nagano Red Cross Hospital, <sup>2</sup>Neurology and Rheumatology, Shinshu University School of Medicine, Nagano, Japan

Conflict of interest: None

A 37-year-old woman admitted to our hospital because of fever, dizziness and cervical lymph node swelling. Neurological examination showed only horizontal gaze nystagmus. Blood test showed low platelet count, hypocomplementemia, anti-nuclear antibody-positive, anti-double-stranded DNA antibody -positive, and anti-aquaporin4 antibody-negative. Cerebrospinal fluid examination showed pleocytosis, high total protein and markedly elevated interleukin-6 concentration. A brain magnetic resonance imaging (MRI) revealed lesion in the medulla oblongata. She was treated with high-dose corticosteroid on the day of admission. After the two hours from the initiation of treatment, the lower paraplegia and hypesthesia appeared. The spinal MRI revealed lesion in the areas from cervical to upper thoracic cord and from central thoracic cord to cone. Lower extremity paraplegia favorably improved after the combination therapy with corticosteroid, immunoabsorption and tacrolimus. [Clinical significance] The patient of this case developed gray-matter myelitis caused by systemic lupus erythematosus (SLE) immediately after the administration of corticosteroid. To provide treatment for SLE-caused myelitis, it is essential to predict subsequent events to initiate aggressive therapy as soon as possible.

## P2-156

### Two cases of lupus panniculitis in our hospital

Takahiro Yuasa, Shohei Makiishi, Taro Miyagawa, Akihiro Sagara, Yasuyuki Shinozaki, Shinji Kitajima, Akinori Hara, Yasunori Iwata, Norihiko Sakai, Miho Shimizu, Kengo Furuichi, Takashi Wada  
Kanazawa University Hospital, Ishikawa, Japan

Conflict of interest: None

[Case 1] A 20 years old female had fever, facial erythema, sunlight hypersensitivity, joint pain and hair loss. Leucocytopenia and anti-nuclear antibody were detected in laboratory date. Thus, she was diagnosed with systemic lupus erythematosus (SLE). When she was 33 years old, she got fever and malaise with subcutaneous nodule on back, hip and upper arm. Skin biopsies from the site revealed that there were lymphocytes and plasma cells in subcutaneous adipose tissue with the necrosis and degeneration of fat cells. She was diagnosed with lupus panniculitis and treated with corticosteroid and tacrolimus. [Case 2] A 25 years old female got joint pain, discoid rash, and sunlight hypersensitivity. A anti-nuclear antibody was detected. Therefore, she was diagnosed with SLE and treated with corticosteroids. She got the pain in the left hip and thigh at 46 years old. The pain became worsen with skin ulcers at 48 years old. Skin biopsies of the lesion showed the necrosis and the calcification of deep fat tissue with small number of inflammatory cells. She was diagnosed with localized lupus panniculitis, and the site was resected surgically. [Conclusion] Herein, we showed 2 cases of lupus panniculitis, which was rare complication of lupus.

## P2-157

### Combination therapy with high dose tacrolimus is effective in the treatment of severe ITP with SLE. - The analysis of three consecutive cases -

Yuya Tabuchi, Kohei Tsujimoto, Iku Shirasugi, Yutaka Shinkawa, Masashi Taniguchi, Mizue Okazaki, Masaaki Fujita, Saori Hatachi, Masato Yagita  
Kitano Hospital, the Tazuke Kofukai Medical Research Institute, Osaka, Japan

Conflict of interest: None

**[Objectives]** SLE is sometimes complicated with severe, refractory immune thrombocytopenia (ITP) with a platelet count less than 20,000/ $\mu$ l. TPO receptor agonists are thought to be often effective, but the long prognosis of them has been unknown. Recently, more and more reports have suggested multi-target therapies using tacrolimus (TAC) are effective in the treatment of lupus nephritis. TAC, which rarely suppresses the bone marrow function and is easily monitored, is a rational therapeutic option for ITP. **[Methods]** We used high dose TAC for all three consecutive patients with severe ITP with SLE. **[Results]** All the patients were able to keep platelets over 20,000/ $\mu$ l. Case 1 was a 47 year-old woman, case 2: a 77 year-old man, and Case3: a 58 year-old woman. The respective minimum platelet counts ( $\mu$ l) were 3,000, 6,000, and 5,000. Case 3 was amegakaryocytic. Although the CH50 levels of case 1 and 3 were normal, that of Case2 was undetectable. We targeted 10 ng/ml for TAC concentration 12 hours after oral use. TAC was used twice daily in case 1 and 3, and once daily in case 2. It took 8 weeks in case 1 and 3, and 6 weeks in case 2 to recover platelets over 20,000/ $\mu$ l. **[Conclusion]** The early use of high dose TAC seems to be effective in the treatment of severe ITP with SLE.

## P2-158

### Thrombotic microangiopathy associated with systemic lupus erythematosus successfully treated with rituximab and plasmapheresis: A case report

Kanako Masuda, Masaki Akimoto, Kakushi Matsushita, Makoto Yoshimitsu, Naomichi Arima  
Department of Hematology and Immunology, Kagoshima University Hospital, Kagoshima, Japan

Conflict of interest: None

A 54-year-old woman was diagnosed with systemic lupus erythematosus (SLE) based on a malar rash, discoid rash, oral ulcers, arthritis, pancytopenia, and a positive anti-dsDNA antibody test result. She was also diagnosed with Sjogren syndrome and collagen disease of the lung. We began treatment with prednisolone (PSL) 20 mg/day, but it was not effective; therefore, we increased the PSL dosage to 30 mg/day and added tacrolimus. High-dose intravenous methylprednisolone was also administered because of stiff joints and muscles, thrombocytopenia, and progression of lung disease. The next day, neurologic symptoms appeared, and magnetic resonance imaging showed an abnormal signal. The severity of thrombocytopenia increased, bilirubin and lactate dehydrogenase levels increased, and fragmented red blood cell count increased to 16%. Thrombotic microangiopathy (TMA) was diagnosed because ADAMTS13 activity was maintained. After double-filtration plasmapheresis was performed 6 times and rituximab (RTX) 375 mg/m<sup>2</sup> was administered 4 times, the severity of thrombocytopenia and hemolysis improved. SLE and the neurologic symptoms also improved. Here, we report a case of TMA associated with SLE that was successfully treated with RTX and plasmapheresis.

## P2-159

### A case of antiphospholipid syndrome presenting with sudden renal failure

Rumiko Miyagi<sup>1</sup>, Haruko Ideguchi<sup>1</sup>, Yoshiaki Ishigatsubo<sup>2</sup>  
<sup>1</sup>National Hospital Organization Yokohama Medical Center, <sup>2</sup>Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine

Conflict of interest: None

A 70-year-old woman was admitted to our hospital with acute kidney injury which started three days ago. Laboratory test results were as follows: BUN37.7mg/dl, Cre2.47mg/dl, P/Cre18.1g/g.cr. She was diagnosed as SLE because of renal failure, lymphopenia (725/mm<sup>3</sup>), anti-dsDNA antibody (47.7IU/ml), anti-nuclear antibody (640 titer), aCL positive and hypocomplementemia. She was treated with intravenous methylprednisolone 0.5g/day for 3 days, and prednisolone (60mg/day). But for worsening renal function, hemodialysis was initiated. On the 13th hospital day, kidney biopsy revealed lupus nephritis IV-G (A/C) and thrombotic mi-

croangiopathy. We diagnosed secondary antiphospholipid syndrome (APS) and added plasma exchange and antithrombotic treatment. On the 25th hospital day, the combination therapy led to renal recovery and the last hemodialysis treatment was given. Catastrophic APS (CAPS) is a rare life-threatening form of APS in which disseminated vascular thrombosis results in multiorgan failure. We report a case of CASP which had effective the combination therapy.

## P2-160

### Large vessel vasculopathy associated with discoid lupus erythematosus (DLE): case report

Daisuke Waki, Akira Onishi, Yuiko Kamei, Kousaku Tsuda, Ikuko Naka, Yo Ueda, Goichi Kageyama, Yoshinori Kogata, Akio Morinobu  
Department of Rheumatology and Clinical Immunology, Kobe University, Kobe, Japan

Conflict of interest: None

[Case] 43-year-old woman came to our hospital complaining of a 7-year history of progressive headache and intermittent claudication. Her past medical history was discoid lupus erythematosus (DLE), which was diagnosed 11 years ago and improved with low dose of prednisolone. She also had a diagnosis of multiple vascular stenosis in the extremities, which was suspected as vasculitis but her symptoms got worse despite of methotrexate administration. After hospitalization, imaging modalities showed luminal narrowing in distal extremity artery, temporal artery and orbital artery. Temporal artery biopsy revealed intimal thickening without inflammatory cells and immunoglobulin deposition in the intima. Therefore, we concluded lupus vasculopathy caused her symptoms. [Clinical significance] To our knowledge, this is the first case of large vessel vasculopathy associated with lupus erythematosus. Lupus vasculopathy is characterized by the deposition of immune globulins and complements in the wall of arteries, resulting in luminal narrowing. Although It had been thought that prefer to occur in small or middle vessel, we have experienced a case of large vessel vasculopathy with DLE, which is thought to be included in the category of lupus vasculopathy.

## P2-161

### A difficult case of childhood-onset systemic lupus erythematosus

Yuko Kurihara, Nobuko Iizuka, Atsushi Suzuki, Takahiro Suzuki  
Department of Internal Medicine, Kawasaki Municipal Hospital

Conflict of interest: None

A 14-year woman was admitted to our hospital because of rash, pancytopenia, class III (A) lupus nephritis and autoimmune hepatitis. She complicated with lupus enteritis. She had massive small intestinal bleeding, so she was transferred to National Center for Child Health and Development. Surgical resection of the small intestine was performed. Her symptoms were improved by treatments with plasmapheresis, pulse steroid, IVCY and MMF. She experienced a seizure. She was improved by treatment with pulse steroid. CV port was placed for TPN and she was discharged. Three months later, she was admitted to our hospital because of sepsis and macrophage activation syndrome. She was improved by treatment with antibiotics, pulse steroid, intravenous CsA, and IVIG, so she was discharged. After one week, she was admitted to our hospital because of CV-port-related infection, so CV port was removed. She was accompanied with lung thrombosis and seizures. She complicated with steroid-induced pancreatitis. She died after suffering sepsis. Childhood-onset SLE have more active disease than adult-onset SLE and higher levels of corticosteroids and immunosuppressive agents are required for disease control. We should keep steroid-related damage in mind.

## P2-162

### Complete abdominal aorta occlusion and severe upper body hypertension in a patient with secondary antiphospholipid syndrome due to systemic lupus erythematosus

Miwa Haranaka<sup>1</sup>, Yasuhiro Kiyonaga<sup>1</sup>, Yuichi Omura<sup>1</sup>, Chiharu Imada<sup>1</sup>, Takashi Ozaki<sup>1</sup>, Hajime Hamasaki<sup>1</sup>, Koji Ishii<sup>1</sup>, Shinji Miyamoto<sup>2</sup>, Hirotaka Shibata<sup>1</sup>

<sup>1</sup>Department of Endocrinology and Metabolism, Rheumatology and Ne-

phrology, Faculty of Medicine, Oita University, Oita, Japan, <sup>2</sup>Department of Cardiovascular Surgery, Faculty of Medicine, Oita University, Oita, Japan

Conflict of interest: None

A 36-year-old man was referred to our hospital for the examination of severe upper body hypertension (systolic blood pressure 230mmHg) and complete abdominal aorta occlusion involving bilateral iliac arteries in May 2014. He had a history of sudden hypertension refractory to several antihypertensive agents since December 2013. The laboratory tests revealed positivity of antinuclear antibody, positivity of antiphospholipid antibodies and low complement levels. Further radiological examination revealed pericardial effusion. Then he fulfilled the 2012 SLICC classification criteria for systemic lupus erythematosus. MRI and PET-CT did not show inflammatory lesions in thoracic aorta including its branches and abdominal aorta. We concluded he had thrombotic occlusion of abdominal aorta caused by antiphospholipid syndrome. He underwent aorto-biiliac bypass surgery with thrombectomy of bilateral renal arteries. The histological specimen revealed thrombotic occlusion but not arteritis. The majority of the thrombotic events associated with APS affect the deep venous system of the lower limbs and arterial thrombosis in some organs. We report a case of complete abdominal aorta occlusion caused by APS. Abdominal aorta occlusion is extremely rare condition in APS.

## P2-163

### Profiles of cell surface proteins of PBMC from patients with SLE

Youhei Nozawa<sup>1,2</sup>, Mitsumi Arito<sup>1</sup>, Manae S. Kurokawa<sup>3</sup>, Seido Ooka<sup>4</sup>, Kazuki Omoteyama<sup>1</sup>, Tomohiro Kato<sup>1</sup>

<sup>1</sup>Clinical Proteomics & Molecular Medicine, St. Marianna University Graduate School of Medicine, <sup>2</sup>Department of Orthopaedic Surgery, Sakuho Municipal Chikuma Hospital, <sup>3</sup>Disease Biomarker Analysis and Molecular Regulation, St. Marianna University Graduate School of Medicine, <sup>4</sup>Division of Rheumatology, Department of Internal Medicine, St. Marianna University Graduate School of Medicine

Conflict of interest: None

**OBJECTIVES** Patients with SLE show diverse clinical manifestations and laboratory findings. A single criterion for the diagnosis of SLE would be useful if it exists. We here investigated cell surface protein profiles of PBMC as a candidate for such a criterion. **METHODS** PBMC from 5 patients with SLE and 5 healthy subjects as a control (HC) were prepared. Only cell surface proteins of living PBMC were biotinylated and then were isolated after cell lysis, using avidin beads. The extracted cell surface proteins were comprehensively analyzed by 2-dimensional fluorescence difference electrophoresis (2D-DIGE). The detected protein profiles were compared between the SLE and HC groups. Further, protein spots differently expressed between the 2 groups were subjected to protein identification by mass spectrometry. **RESULTS** In total, 468 protein spots were detected by 2D-DIGE. We found that intensity of 137 protein spots (29.3%) showed more than  $\pm 1.5$ -fold difference between the 2 groups. Among them, intensity of 44 protein spots (9.4%) showed more than  $\pm 2.5$ -fold difference. 17 out of the 44 protein spots were identified until now. **CONCLUSIONS** Cell surface protein profiles of PBMC were different greatly between SLE and healthy subjects. The profiles would be a single criterion candidate for SLE.

## P2-164

### Efficacy of high dose Beraprost and maintenance immunosuppressive therapy in early $\alpha$ -Scl-70 antibody (Ab) (+) systemic sclerosis (SSc)

Jiro Yamana, Katsuhiko Oi, Rie Sasaki, Mitsuhiro Iwahashi, Seizo Yamana  
Higashi-Hiroshima Memorial Hospital

Conflict of interest: None

[Objectives] The prognosis of  $\alpha$ -Scl-70-Ab (+) SSc patients with pulmonary hypertension is still poor because of complicated pulmonary fibrosis. Any qualified disease modifying therapy for this disease does not exist. Here, we shows the efficacy of high dose Beraprost and mainte-

nance immunosuppressive  $\alpha$ -Scl-70-Ab (+) SSc. [Methods] 6 cases of  $\alpha$ -Scl-70-Ab (+) SSc with pulmonary fibrosis who visited our out patients clinic after 2009 and administered with more than 180ug of Beraprost and maintenance immunosuppressive therapy such as Azathioprine or Tacrolimus at early stage are analyzed. 11 cases of  $\alpha$ -Scl-70-Ab (+) SSc who visited our hospital after 2009 are enrolled as control. [Results] The mean disease duration of 6 cases is 5.5 years at the end of observation. The serum levels of KL-6 were decreased in all cases and %VC were increased. No digital ulcer observed in all cases, while two patients developed digital ulcers and one patient died with progressive lung disease. [Conclusions] High dose Beraprost and maintenance immunosuppressive therapy could be effective in  $\alpha$ -Scl-70-Ab (+) SSc patient with lung fibrosis at early stage. Long-term safety and efficacy need to be evaluated to improve 20-years-survival of patients who is suffered from this miserable disease.

## P2-165

### Diffuse cutaneous systemic sclerosis with scleroderma renal crisis occurring after the use of paclitaxel for ovarian cancer

Toshihiro Tono, Takeo Kudo, Hiroaki Taguchi, Yasuo Osone, Yutaka Okano

Department of Rheumatology, Kawasaki Municipal Hospital, Kawasaki, Japan

Conflict of interest: None

A case of systemic sclerosis in a 62-year-old woman who was received paclitaxel for the treatment of an ovarian cancer. She was diagnosed to be suffering from ovarian cancer stage IV in March 2013, and received chemotherapy with paclitaxel and carboplatin (8 courses). In February 2014 she was referred to our hospital as she developed thickening of the skin on the limbs with Raynaud's episodes. Serological tests showed antinuclear antibodies (ANA)  $\times 80$  (speckled type), anti-RNA polymerase III antibodies 134.0 Index (normal:  $<28$ ) were elevated. She was diagnosed as diffuse cutaneous systemic sclerosis. In June 2014 she was admitted to our hospital due to progressive dyspnea and renal dysfunction. She was diagnosed as scleroderma renal crisis and finally this patient died of a respiratory disorder. Autopsy findings confirmed the presence of wall thickness of interlobular arteries of kidney. Recently, there have been a number of case reports linking paclitaxel to the development of scleroderma and scleroderma like changes. However, to our knowledge, this is the first known case of a patient with serologically and pathologically confirmed systemic sclerosis complicated with scleroderma renal crisis secondary to paclitaxel use.

## P2-166

### Successful treatment of scleroderma renal crisis using angiotensin converting enzyme (ACE) inhibitor and Bosentan

Yuichi Yokoyama, Aki Nishioka, Takeo Abe, Chie Ogita, Tetsuya Furukawa, Takahiro Yoshikawa, Takuya Hino, Atsushi Saito, Masahiro Sekiguchi, Naoto Azuma, Masayasu Kitano, Shinichiro Tsunoda, Kiyoshi Matsui, Hajime Sano

Division of Rheumatology of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan

Conflict of interest: None

A 77-years-old man was admitted to our hospital because of dermal sclerosis and repeated pericardial effusion. On physical examination, he was noted advanced skin curing. Immunological test show anti-RNA polymerase 3 antibody was over 150U/ml. A laboratory examination of pericardial effusion revealed anti-RNA polymerase 3 antibody was over 150U/ml. We diagnosed diffuse cutaneous systemic sclerosis (SSc) and pericarditis due to SSc. He started to take oral prednisone at a dose of 20 mg/day, and pericardial effusion lost. After started prednisone, his systolic blood pressure reached 150mmHg. Laboratory test showed an elevated serum level of creatinine at 1.86mg/dl. Renal biopsy showed marked intimal thickening and narrowing of the small arteries, and atrophic tubules and interstitial fibrosis. He was diagnosed scleroderma renal crisis (SRC). Oral administration of Imidapril immediately normalized his blood pressure but his serum creatinine didn't decrease. He started to take Bosentan and his serum level of creatinine decrease to 1.40mg/dl. It was reviewed

that endothelin-1 (ET-1) levels, the tissue expression of ET-1 ligand and receptor, safety and efficacy of Bosentan in SRC. We report a case of SRC using ACE inhibitor and Bosentan from pathological point of view.

## P2-167

### Success in avoiding maintenance dialysis through plasma exchange in a case of scleroderma renal crisis

Taro Fujisawa, Masami Mizuno, Takuo Hirota, Yukio Horikawa, Jun Takeda

Department of Immunology & Endocrinology, Gifu University Hospital, Gifu, Japan

Conflict of interest: None

A 69-year-old woman developed bilateral finger joint pain in 2008. In 2013, Raynaud phenomenon, bilateral finger joint swelling, and skin sclerosis of the fingers and the part distal to the forearm appeared. She consulted us and anti-Scl-70 antibody was positive, leading to a diagnosis of systemic scleroderma. Outpatient treatment with oral prednisolone (5 mg/day) was started for arthralgia. In August 2014, she was emergently transported to our hospital because of nausea and malaise. On arrival, she had a blood pressure of 204/104 mmHg, low platelet count, renal dysfunction, and hemolysis signs. She was hospitalized with a diagnosis of scleroderma renal crisis (SRC) and thrombotic microangiopathy (TMA). In addition to captopril treatment, she was started on plasma exchange (PEX) with fresh frozen plasma (FFP). After 7 sessions of PEX (including those for 5 straight days), platelet count normalized, allowing maintenance dialysis to be avoided. Introduction of antihypertensive therapy with short-acting ACE inhibitors has dramatically improved survival and renal prognosis in patients with SRC, although 5-year survival rate is still about 60%. TMA is reportedly present in about 60% of SRC cases. PEX with FFP has recently been reported to be useful in treating SRC complicated by TMA.

## P2-168

### Acute renal failure in systemic sclerosis

Yuri Sadanaga<sup>1</sup>, Yukihide Ono<sup>1</sup>, Yukiko Tokuda<sup>1</sup>, Satoko Tashiro<sup>1</sup>, Rie Suematsu<sup>1</sup>, Nobuyuki Ono<sup>1</sup>, Syuichi Koarada<sup>1</sup>, Yoshifumi Tada<sup>1</sup>, Akihide Ohta<sup>2</sup>, Yutaka Chifu<sup>3</sup>

<sup>1</sup>Department of Rheumatology, Faculty of Medicine, Saga University, Saga, Japan, <sup>2</sup>Department of Adult and Gerontological Nursing, Faculty of Medicine, Saga University, Saga, Japan, <sup>3</sup>Saiseikai Karatsu Hospital

Conflict of interest: None

**Objective:** The aim of this study was to analyze clinical features, treatment and outcome of acute renal failure (ARF) in patients with SSc. **Methods:** Patients with SSc who developed ARF between 1996 and 2014 were reviewed. **Result:** Six patients (2 males) were identified. Among 6 patients, 4 showed high blood pressure when their renal damage developed. Two were normotensive; one was MPO-ANCA positive and showed crescentic glomerulonephritis by a renal biopsy, and the other developed thrombocytopenia, hemolytic anemia associated with elevated serum von Willebrand factor, diagnosed as having thrombotic microangiopathy (TM). Patients with hypertensive renal failure were treated with angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers, and Ca-blockers. Corticosteroids were given to the patient with ANCA-associated renal failure. A patient with normotensive renal failure with TM was treated by ACEi, plasma exchange, and recombinant thrombomodulin. Among patients with hypertensive renal crisis, 2 died, and 2 required hemodialysis. **Conclusion:** ARF in systemic sclerosis developed by some different mechanisms. It is important to identify the mechanism and select appropriate treatments.

## P2-169

### A case of MPO-ANCA positive systemic scleroderma (SSc) with diffuse alveolar haemorrhage (DAH)

Ami Matsumoto, Okinori Murata, Nobuhito Sasaki, Yuka Oikawa, Kouko Kowata, Yukari Ninomiya, Hitoshi Kobayashi, Kohei Yamauchi  
Division of Pulmonary Medicine, Allergy, and Rheumatology, Department of Internal Medicine, Iwate Medical University School of Medicine,

Iwate, Japan

Conflict of interest: None

Reportedly MPO-ANCA was positive in some cases of SSc and complicated ANCA-associated vasculitis (AAV) which might cause DAH and rapidly progressive glomerulonephritis. Therefore these cases had a poor prognosis. A 56-year-old woman was receiving the treatment for SSc with interstitial pneumonia and chronic respiratory failure. She presented with fever, bloody sputum with dyspnea. Hypoxemia and anemia were indicated. A chest radiograph showed bilateral infiltrative shadows in addition to interstitial pneumonia. A chest computed tomograph showed bilateral consolidation. The findings from bronchial alveolar lavage fluids (BALF) showed bloody and presence of siderophores, therefore, she was diagnosed DAH. Renal dysfunction was not indicated. The level of MPO-ANCA was elevated. In this regard, we thought that this case was SSc complicated with AAV. Treatment was started with pulse therapy of methylprednisolone and pulse therapy of cyclophosphamide followed by oral prednisolone 40mg/day. After these treatments, her respiratory condition improved and chest infiltrative shadows disappeared. The level of MPO-ANCA was decreased. When DAH is complicated with MPO-ANCA-positive SSc, it was suggested that the strong immunosuppressive therapy would be important against concurrence of AAV.

## P2-170

### Systemic sclerosis with anti-RNA polymerase III showing scleroderma renal crisis caused by low-dose glucocorticoid treatment

Hiroki Kono, Hirofumi Watanabe, Ayuko Sogabe, Takaki Nojima, Satoshi Yamasaki, Kazuhiko Kumagai, Eiji Sugiyama

Department of Clinical Immunology and Rheumatology, Hiroshima University Hospital, Hiroshima, Japan

Conflict of interest: None

A 57-year-old woman, who had been diagnosed as systemic sclerosis with anti-RNA polymerase III antibody, was admitted to our hospital because of nausea and headache. She has been treated with 10mg prednisolone (PSL) for the treatment of progressive sclerosis of skin from 2 months before hospitalization. After then, her BP gradually rose with renal dysfunction. On admission, BP was elevated to 202/100mmHg. Laboratory data showed renal dysfunction (eGFR 32 mL/min/1.73m<sup>2</sup>), thrombocytopenia and hemolytic anemia. From these findings, she was diagnosed as scleroderma renal crisis (SRC) with thrombotic microangiopathy, and treated with captopril, nifedipine, and Doxazosin mesylate. After then, her BP gradually fell to normal with improvement of renal dysfunction and hemolytic anemia. [Clinical significance] Patients at high risk of developing SRC have been reported to be those with rapid progression of sclerosis, recent treatment of high dose glucocorticoid (> PSL 15mg) or an anti-RNA polymerase III antibody. However, doses of glucocorticoid associated with SRC seem to be still controversial. We report here the case of systemic sclerosis developing SRC just after treatment of only 10 mg PSL, and discuss the relation of SRC with glucocorticoid treatment.

## P2-171

### A case of renal crisis and TMA of scleroderma treated with plasma exchange therapy

Takamasa Nozaki, Yosuke Nagasawa, Kaita Sugiyama, Atsuma Nishiwaki, Natsumi Ikumi, Hidetaka Shiraiwa, Hiromi Karasawa, Mitsuhiro Iwata, Hitomi Haraoka, Noboru Kitamura, Yoshihiro Matsukawa, Masami Takei

Division of Hematology and Rheumatology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

Conflict of interest: Yes

The patient was 41-year-old woman. She had Raynaud's phenomenon but she was not definitive diagnosis in 2009. She consulted hospital with coughing. Examination revealed hemolytic anemia, thrombocytopenia, renal dysfunction. Heart failure was complicated. She had diagnosed as thrombotic thrombocytopenic purpura (TTP) and acute renal failure. She was conducted with plasma exchange and hemodialysis for 4days

but not improved. She was transferred to our hospital at June 27. We diagnosed scleroderma by ANA×640 (Nucleolar), skin curing and skin biopsy. We considered to renal crisis and thrombotic microangiopathy disease (TMA) by 3.7% crushed red blood cells, haptoglobin <10mg / dl, ADAMTS 19 85.3%, or from TTP than renin activity 73ng / ml. We conducted with plasma exchange and hemodialysis at 18 times. Her percent fragmented red blood cells was reduced to 0.2 percent. TMA is complicated with SLE, scleroderma in rheumatic disease. Especially it is complicated with half pathient of renal crisis in scleroderma. Therapy of it is plasma exchange.

## P2-172

### Analysis of treatments for scleroderma with interstitial pneumonitis

Sara Murakami, Yuta Yamaguchi, Shuzo Yoshida, Madoka Morimoto, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa  
Department of Internal Medicine (I), Osaka Medical College, Osaka, Japan

Conflict of interest: None

[Objectives] To evaluate the efficacy and renal damage of azathioprine (AZP) or tacrolimus (TAC) in scleroderma patients with interstitial pneumonitis (SSc-IP). [Methods] We analyzed the prognosis and clinical findings of patients with SSc-IP treated with AZP or TAC in our hospital between 2002 and 2013. [Results] Out of 157 patients with SSc-IP, there were 23 in AZP group (63.58±11.4mg/day) and 13 in TAC group (3.18±0.91mg/day), 7 males and 29 females, with a median age (interquartile range) of 66 yrs (range: 53-73 yrs). The 5-year survival rate after the start of treatment was 96% and 1 patient died of bladder cancer. KL-6 value in TAC group was significantly higher than in AZP group (959 (707-1648) vs 627 (423-927), p=0.04). KL-6 value decreased during treatment in TAC and AZP groups, and there was no significant difference of the changes of KL-6 after the treatment between these groups. Creatinine levels in TAC and AZP groups did not increase after the treatment. [Conclusion/Discussion] There were no significant differences of clinical results between AZP and TAC groups, suggesting the equal efficacy.

## P2-173

### 1 example of clinically amyopathic dermatomyositis <CADM>, MDA-5-antibody was positive, delayed treatment intervention caused the unfortunate outcome

Kota Azuma, Takeo Abe, Aki Nishioka, Chie Ogita, Yuichi Yokoyama, Tetsuya Furukawa, Takahiro Yoshikawa, Takuya Hino, Atsushi Saito, Masahiro Sekiguchi, Naoto Azuma, Masayasu Kitano, Shinichiro Tsunoda, Kiyoshi Matsui, Hajime Sano  
Division of Rheumatology Department of Internal Medicine Hyogo College of Medicine

Conflict of interest: None

[Introduction] It is easy to merge the rapidly progressive interstitial pneumonia in CADM, MDA-5 antibody-positive, We should perform the strong immunotherapy. [Case] 64-year-old, female, chief complaint wrist pain. H26.5 beginning around, wrists of pain and difficult to climb the stairs appeared. It was said that collagen disease suspicion because it was recognized reverse Gottron signs. So Dermatomyositis is suspected. Then general malaise exacerbation, also symptoms such as exertional dyspnea worsened, she entered hospital. WBC2720, RBC4320000, Plt160000, IgG1550, IgM79, CEA6.6, ANA40 times (Ho), ARS antibody-negative, SP-D83.5, KL-6 739. Lung field is evident IP is not recognized, findings of scattered pleurisy were the main. The diagnosis of dermatomyositis, it was started with PSL20mg/day. MDA-5 antibody positive and recognizing IP exacerbation in chest CT made her re-hospital. After admission mPSL pulse 500mg×3days 4course, IVCY500mg-4course, between the mass immunoglobulin therapy 5days Tac oral, and also performs plasma exchange 5times, she dead by respiratory failure. [Clinical significance] If it is strongly suspected CADM, We must do strength treatment, in addition to a steroid pulse therapy, it is necessary to perform a triple therapy of immunosuppressive agent (CPA + Tac).

## P2-174

### Pulmonary hypertension in a patient with anti-Jo-1 syndrome

Sara Murakami<sup>1</sup>, Yuta Yamaguchi<sup>1</sup>, Akihiko Nakabayashi<sup>1</sup>, Madoka Morimoto<sup>1</sup>, Kazushi Konma<sup>1,2</sup>, Yoshinori Katada<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Sakai City Hospital, Sakai City, Japan,

<sup>2</sup>Sakai City Hospital

Conflict of interest: None

[Case] A 70-year old male patient was admitted to our hospital for dyspnea. Interstitial pneumonia had been pointed out on his mass chest x-Ray for 10 years. He developed dyspnea gradually since then. Half a year before admission, he went to the National Cerebral and Cardiovascular Center, where diagnosis of severe pulmonary hypertension (mean pressure: 52 mmHg) was made. He was referred to our hospital for evaluation concerning autoimmune diseases. Although antinuclear antibody (ANA) and anti-Jo-1 antibody was positive, he did not have any other signs for neither myositis nor other autoimmune diseases except interstitial pneumonia. With the diagnosis of undifferentiated connective tissue disease (UCTD) with pulmonary hypertension, he was treated with 70mg of PSL and 100 mg of cyclophosphamide. The pulmonary artery mean pressure decreased to 27 mmHg and his dyspnea ameliorated. [Discussion] Pulmonary hypertension complicated with UCTD could be successfully treated with combination of steroid and cyclophosphamide. Only one similar case, anti-Jo-1 syndrome, has been reported to date (Arthritis Care Res. 2010 Mar;62 (3):425-9).

## P2-175

### A case of clinically amyopathic dermatomyositis with meningioma treated by resection it

Takuya Hino, Takeo Abe, Kota Azuma, Chie Ogita, Yuichi Yokoyama, Tetsuya Furukawa, Takahiro Yoshikawa, Atsushi Saito, Aki Nishioka, Masahiro Sekiguchi, Naoto Azuma, Masayasu Kitano, Shinichiro Tsunoda, Kiyoshi Matsui, Hajime Sano

Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine

Conflict of interest: None

[Case report] A 70-year-old woman was admitted into the hospital because of muscle weakness and cutaneous rash. She had been well 6 months before. She developed progressive muscle weakness gradually and she got rash of the hand and face. Her skin biopsy showed she contracted dermatomyositis (DM). The results of laboratory tests on admission were: Anti Jo-1 antibody negative, CPK 93, CRP 1.3. CT of the chest and abdomen, ultrasonography of the abdomen and endoscopy findings were normal. We diagnosed her as clinically amyopathic dermatomyositis (CADM) from her typical Gottron's papule and heliotrope rash. We found anti MDA-5 antibody was positive a few days after. The patient was treated with prednisolone (40mg/day), tacrolimus and cyclophosphamide (500mg bi-weekly) but her muscle strength didn't increase and her rash got worse. A month she delired. CT and MRI revealed the presence of left frontal mass. The surgical resection of the tumor, the histology showed a meningioma. After the operation her rash got better significantly. [Discussion] There is no clear association between DM and meningioma. There is no case report of DM with meningioma in Japan. [Clinical significance] How Anti MDA-5 antibody works is not unclear. This case may make the mechanism clear.

## P2-176

### Successful treatment of cutaneous ulcers with mycophenolate mofetil in patients with anti-CADM-140 / MDA5 antibody positive dermatomyositis

Shinichi Nogi, Takayoshi Kurabayashi, Sho Sasaki, Yasushi Koyama, Noriko Sasaki, Naofumi Chinen, Kiri Honda, Chiho Yamada, Shinji Sato, Yasuo Suzuki

Department of Internal Medicine, Division of Rheumatology, Tokai University School of Medicine

Conflict of interest: None

[Case] A 44 year-old woman noticed erythema in fingers, anterior



chest, and dorsal region since September 2013. She visited our hospital in March 2014. She was diagnosed as clinically amyopathic dermatomyositis (CADM) because she had heliotrope rash, Gottron's sign and interstitial lung disease without obvious muscle weakness and elevation of serum creatine kinase. Blood analysis revealed she had anti-CADM-140/MDA5 antibody and treatment with methyl- prednisolone (PSL) pulse therapy followed by 60 mg of PSL and 3mg of tacrolimus daily was initiated for rapidly progressive interstitial lung disease (RP-ILD). She was discharged with 40mg of PSL daily because her respiratory symptoms were improved rapidly although interstitial change in chest CT remained the same. As her cutaneous ulcers over the metacarpophalangeal joints were getting worse with decreasing amount of PSL. We started 500mg of mycophenolate mofetil (MMF) on April 2014 and raised the dose up to 1500mg daily. Cutaneous ulcers improved at 2 months after the initiation of MMF in accordance with the improvement of interstitial change of CT. Anti-CADM-140/MDA5 titer also fell to below the cutoff level at the same period.

## P2-177

### **The case of CADM with interstitial pneumonia, which was improved by any therapies, various immunosuppressive therapy, IVIG, endotoxin adsorption therapy**

Takao Katsuragawa, Takumi Matsumoto, Hiroaki Tamura  
Kinikyou Central Hospital

Conflict of interest: None

{Case} 50's Woman {Clinical course} She felt polyarthralgia and rash in December certain year, and next month she was admitted our hospital. The rash seemed dermatomyositis's rash and IP was seen on CT. Myogenic enzyme elevated a little (CK48, Aldrase7.1), but anti JO-1 antibody was positive and skin biopsy showed pathological findings of DM, so we diagnosed her CADM. KL-6 was 262. On January 20 we administered PSL40mg and tacrolimus (TAC) 3mg. Then symptom was improved. On the end of April IP became worse (KL-6: 1730), DAD was suspected on CT. On 1 May we started M-PSL pulse and IVCY, and PSL50mg and ciclosporin200mg was prescribed. Breathing became worse so oxygen administration (3L) was need. We continued IVCY (500mg) per 2weeks and IVIG was added on 7 June but KL-6 elevated to 2300 and respiratory status did not improve. On 17 June we started endotoxin adsorption therapy (Polymyxin B column was used for 2days) and we continued IVCY per 2weeks and IVIG per 4weeks. After these treatment KL-6 decreased and respiratory status recovered, then she was discharged. {Conclusion} The case of CADM with IP worsened despite of under treatment with PSL and TAC, but after some treatments include endotoxin adsorption therapy, diseased has improved. Endotoxin adsorption therapy might be effective

## P2-178

### **Two cases of clinically amyopathic dermatomyositis (CADM) treated by multidisciplinary treatment**

Kosuke Fukuda, Toshiyuki Aramaki, Kaoru Terada, Yukitaka Ueki  
Rheumatic Disease Center, Sasebo Chuo Hospital, Nagasaki, Japan

Conflict of interest: None

[Case1] A 42-year-old woman visited the previous hospital for rash, arthralgia and myalgia. The patient was diagnosed as dermatomyositis and treated with intravenous methylprednisolone (mPSL) pulse, oral prednisolone and cyclosporine. However she had relapsed rash and arthralgia after a month, and she showed dyspnea. She transferred to our hospital and we found she presented rapid progressive interstitial pneumonia (RPIP). Then, she was diagnosed as CADM and treated with mPSL and intravenous cyclophosphamide (IVCY) pulse. Her respiratory symptom got so worse that we added leukocytapheresis. After the therapies the symptom didn't get worse. [Case2] A 58-year-old man visited the previous hospital for fever and dry cough. He was diagnosed interstitial pneumonia. He was referred to our hospital and we found he presented reverse Gottron's papule and RPIP. He was diagnosed as CADM and treated with mPSL and IVCY. His respiratory symptoms were so progressive that we added endotoxin adsorption therapy. Nevertheless he showed the symptoms of mediastinal emphysema after therapies, his condition got

improved. Although CADM is often resistant to treat due to RPIP, we successfully treated by multitargeting immunosuppressive therapy and blood perfusion therapy.

## P2-179

### **A case of Dermatomyositis associated interstitial pneumonia complicated with pneumomediastinum successfully treated with cyclophosphamide and tacrolimus**

Kumiko Umemura<sup>1</sup>, Kahori Oshima<sup>1</sup>, Takakazu Hasegawa<sup>1</sup>, Syunsuke Yokoi<sup>1</sup>, Michita Suzuki<sup>1</sup>, Kyoko Takano<sup>1</sup>, Eiji Nagasawa<sup>3</sup>, Nobuyoshi Minemura<sup>2</sup>, Masao Katayama<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, National Hospital Organization Nagoya Medical Center, Nagoya, Japan, <sup>2</sup>Department Of Internal Medicine, Tamazensyoen, National Sanatorium, Tokyo, Japan, <sup>3</sup>Nagasawa Clinic, Nagoya, Japan

Conflict of interest: None

[Objectives] We report a case of dermatomyositis associated interstitial pneumonia complicated with pneumomediastinum successfully treated with cyclophosphamide and tacrolimus. [Methods] A 45-year-old man was admitted to our hospital, because of interstitial pneumonia. He received steroid pulse therapy. After steroid pulse therapy, prednisolone (PSL) 50mg/day was started, and discharged. 4 months later, thus lung involvement didn't improve, cyclosporine (CyA) was added to PSL 25mg/day. CyA couldn't continue, because side effects, such as dizziness and liver dysfunction, was appeared. 1 month later, his respiratory symptoms worsened, computed tomography showed progression of interstitial pneumonia and pneumomediastinum. Physical examination, Gottron's sign was found, and we diagnosed him Dermatomyositis (DM). Serum CK level was normal, and he didn't have any muscle symptoms. [Results] PSL was increased to 50mg/day, and cyclophosphamide pulse therapy (IVCY) was administered. We added tacrolimus (TAC) 4mg/day. Total six times IVCY, interstitial pneumonia and pneumomediastinum was improved. [Conclusion] Pneumomediastinum is a poor prognosis of dermatomyositis associated interstitial pneumonia. We report the efficacy and safety of IVCY and TAC.

## P2-180

### **Intravenous immunoglobulin therapy as an effective treatment for steroid-resistant dermatomyositis with early dysphagia: a case report**

Makoto Inoue

Inoue Hospital

Conflict of interest: None

We present herein an interesting case of dermatomyositis with early dysphagia in which repeated administration of Intravenous immunoglobulin therapy improved dysphagia and restored ambulatory function. Related literature is also reviewed. A 60-year-old woman had experienced dyspnea, cough, muscle weakness, and rash on limbs since around January 2014 and was referred to our institution for further examination and treatment in February 2014 after examination by her local doctor could not identify the cause. On admission, findings of rash; muscle weakness; arthritis; slightly elevated creatinine kinase (CK) levels on blood testing; myositis on magnetic resonance imaging; and interstitial pneumonia on computed tomography led to a diagnosis of dermatomyositis. Although CK elevation was mild, dysphagia was evident from an early stage and limb muscle weakness was advanced; therefore, a combination of steroid pulse therapy, steroid therapy and tacrolimus therapy was administered. No improvements were observed and the patient remained unable to eat with ADL limited to turning over in bed. Severe myositis was subsequently diagnosed and high-dose gamma globulin therapy was performed, after which dysphagia improved and ambulatory function returned.

## P2-181

### **A case of dermatomyositis with gastric and breast cancer**

Junya Yamahana

Department of Internal Medicine, Toyama Prefectural Central Hospital

Conflict of interest: None

A 60 year old woman suffered from muscle weakness and pain of upper arms followed by Raynaud's phenomenon. Heliotrope rash was found on both eyelids, and the muscular strength test decreased with MMT 3/5. Blood examination showed elevation of myogenic enzymes; creatine kinase (CK) 7525 IU/L, AST 273 IU/L, ALT 156IU/L, and LD 1,004IU/L. MR imaging revealed inflammation of bilateral femoral muscle MRI, and Electromyography showed myogenic change. Taken together she was diagnosed as dermatomyositis. Closer inspection revealed overlap of cancers of stomach breast. Prednisolone (PSL) 60 mg (1 mg/kg)/ day after total gastrectomy, mastectomy and sentinel lymph node resections. However, muscular strength decreases to MMT 1/5, improvement of the CK remained about 5,000IU/L. Although methylprednisolone pulse therapy (0.5g, 3days) was done, swallowing difficulty, and pneumonia were appeared, respirator management was needed. High dose  $\gamma$ -globulin therapy (25 g, 5 days) was performed. After the treatment, muscular strength improves MMT 4/5, CK to 140IU/L, and she could leave from respirator management. Our case suggests the effectiveness of high dose  $\gamma$ -globulin therapy for steroid-resistant dermatomyositis.

### **P2-182**

#### **Rituximab for treatment of 3 cases with refractory Dermatomyositis/ Polymyositis**

Yoshihiko Murakami, Seido Ooka, Hisae Ohjimi, Kana Ishimori, Shoshi Shinagawa, Hiromi Matsushita, Hidenori Mikage, Teisuke Uchida, Hirofumi Mitomi, Machiko Mizushima, Hiroshi Ito, Yoshioki Yamasaki, Takahiro Okazaki, Hidehiro Yamada, Shoichi Ozaki  
St. Marianna University School of Medicine Hospital

Conflict of interest: None

We experienced refractory dermatomyositis/polymyositis (DM/PM) who were successfully treated with Rituximab (RTX). 1st case was 56 year old female. She realized muscle weakness and was diagnosed PM, interstitial pneumonia (IP). CK elevated to 5,960 U/L. After steroid pulse and immunosuppressive therapy, CK normalized but immunosuppressant was discontinued because of hepatotoxicity. PM relapsed and CK elevated to 1,442 U/L. After steroid pulse and RTX 650mg/week (4 times), CK and muscle weakness improved. 2nd case was 42 year old male. He realized myalgia and muscle weakness. CK elevated to 1,014 U/L. He was diagnosed DM, IP. Steroid pulse, intravenous immunoglobulin (IVIG), intravenous cyclophosphamide (IVCY) were administered but were ineffective. After RTX 700mg/week (3times), CK, myalgia and muscle weakness improved. 3rd case was 43 year old female. She realized skin rash on extremities and myalgia. CK elevated to 277 U/L. She was diagnosed DM, IP. After steroid pulse and IVCY, CK normalized but IVCY was discontinued because of hepatotoxicity. DM relapsed and CK elevated to 217 U/L. IVIG was ineffective. After RTX 500mg/week (2 times), CK, skin rash and myalgia improved. RTX could be an alternative therapy for refractory DM/PM.

### **P2-183**

#### **Two cases of interstitial lung disease in dermatomyositis treated with rituximab and multiple immunosuppressants**

Yutaro Soejima, Saori Sakaue, Mikiko Shinozaki, Noboru Hagino  
Teikyo University Chiba Medical Center

Conflict of interest: None

[Objectives] To report the effect of rituximab and multiple immunosuppressant use in dermatomyositis-interstitial lung disease (DM-ILD) [Methods] Observational report of 2 cases [Results] Case 1: 69y.o F with DM-ILD, treated with mPSL pulse therapy, IVCY, Rituximab and Tocilizumab. Her ILD didn't respond to those treatment and patient died on day 18. anti-MDA5 antibody positive. Case 2: 65y.o F with DM-ILD, treated with mPSL pulse, IVCY, Rituximab and Tacrolimus continuous infusion. Her ILD slightly responded to these treatment. [Conclusion] DM-ILD is difficult to treat despite of these intensive therapy. Further optimal treatments need to be investigated.

### **P2-184**

#### **A case of refractory polymyositis (PM) successfully treated with abatacept (ABT)**

Keiji Komura, Ryota Yoshimoto, Katsutoshi Mizumoto, Kouhei Eguchi, Daisuke Fujishiro, Satoru Kodama, Atsushi Kobayashi, Kensaku Okamoto, Yuichi Makino, Masakazu Haneda  
Division of Metabolism and Biosystemic Science, Department of Internal Medicine, Asahikawa Medical University

Conflict of interest: None

Recently the efficacy of biologic agents for refractory myositis has been reported. We present a refractory case of PM improved after administration of ABT. A 32-year-old man was admitted to our hospital in August 2008 due to markedly elevated serum CK level with muscle weakness. A diagnosis of PM was made by muscle biopsy and other examinations. High-dose steroid therapy was started, and then methotrexate, azathioprine, cyclosporine A and intravenous immunoglobulin (IVIG) was administered alone or in combination with each other, but effect on his symptom and CK level was limited and exacerbation by tapering of PSL dosage was repeated. In January 2011, he was admitted to our hospital, and malignancy and other myopathy was excluded by re-examinations. Then, we used monthly IVIG, tacrolimus, mycophenolate mofetil, or intravenous cyclophosphamide therapy, but CK level was elevated between 5000 and 8000 IU/L, and muscle weakness was gradually worsened. Therefore, we decided to use ABT, and it was administered from January 2013 after obtaining an informed consent. The CK level begun to decrease and muscle strength was gradually recovered from July 2013. After June 2014 CK level was decreased to 1000 IU/L level and tapering of PSL dosage to 15 mg/day became possible.

### **P2-185**

#### **An autopsy case of granulomatosis with polyangiitis that showed pathological remission**

Shuzo Sato, Hiroko Kobayashi, Tomoyuki Asano, Eiji Suzuki, Hiroshi Watanabe, Hiromasa Ohira  
Department of Gastroenterology and Rheumatology, Fukushima Medical University School of Medicine, Fukushima, Japan

Conflict of interest: None

A 72-year-old man, who had a diagnosis of granulomatosis with polyangiitis (GPA) by renal and nasal mucosa biopsy at 57-year-old, died suddenly. He had been treated with prednisolone and cyclophosphamide, but he had been suffered from recurrent hemoptysis accompanied with nodular cavity infiltrates in both lungs. His creatinine levels had been gradually increased. Autopsy showed he died of pulmonary embolism. Cavities with scars were noted in the lungs, and focal and segmental glomerulosclerosis and atrophic tubules were noted in the kidneys, but there were no active granulomatous lesions or vasculitis. It is difficult to define a clinical remission in GPA. This patient had been treated with immunosuppressants until his death because he had been considered to be in an active stage of GPA, but pathological findings suggested that he was in a remission stage. This case is notable to discuss clinical and pathological remission in GPA.

### **P2-186**

#### **Intravascular large B-cell lymphoma with a high titer of PR3-ANCA mimicing granulomatosis with polyangiitis**

Yutaka Shinkawa, Saori Hatachi, Masato Yagita  
Department of Clinical Immunology and Rheumatology, the Tazuke-Kofukai Medical Research Institute, Kitano Hospital, Osaka, Japan

Conflict of interest: None

[case] A 63-year-old man had presented with intermittent fever for 2 month. Laboratory data showed pancytopenia, high level of LDH, ferritin, and sIL-2R. There were no lymphadenopathy in CT scan. The bone marrow aspiration did not reveal abnormal lymphoid cells. As the possibility of intravascular large B-cell lymphoma (IVLBCL) could not be excluded, random skin biopsy was performed. On the other hand, immunologic studies showed the elevated level of PR3-ANCA (222 U/ml). MRI

of the brain showed sinusitis, otitis, and hypertrophic pachymeningitis. From these findings, the presence of limited granulomatosis with polyangiitis (GPA) was suspected. We started the oral administration of prednisolone (1mg/kg/day). In the next day, the result of both nasal mucosal biopsy and random skin biopsy revealed the growth of CD20 positive lymphoid cells within the intra-vascular spaces. The diagnosis of IVLBCL was made. The patient was treated with R-CHOP. However, the chemotherapy was discontinued after three courses because of adverse events. After six months, the recurrence of IVLBCL was noticed. [Conclusion] There has been three reports regarding on ANCA-positive IVLBCL. We summarize the characteristics ANCA positive IVLBCL including our case.

## P2-187

### Culture-negative infectious endocarditis with positive antiproteinase 3 antibodies

Chiai Nakata, Tomoo Murayama, Eishi Uechi, Yoshiki Shiohira  
Department of Rheumatic Diseases, Tomishiro Central Hospital, Okinawa, Japan

Conflict of interest: None

[Case] A 53-year old man with intermittent fever for 1 year, lung nodules, hematuria, proteinuria and positive serology for PR3-ANCA was admitted. Infectious diseases were negative in the imaging tests, the serological tests, and the cultivation tests. An abnormal structure was in the tricuspid valve in the transthoracic echocardiography. But cardiologist took it as the normal range. In the lung biopsy, granulomatous vasculitis with necrosis was seen. We diagnosed the patient GPA, and started IVCY pulse therapy and high-dose steroid. After start of therapy, the patient improved immediately and serum CRP was normalized. After 83 days from the start of therapy, serum CRP rose and vegetations on the tricuspid valve was seen in the transthoracic echocardiogram. And vegetation was confirmed to tricuspid valve by the operation. Histopathological assessment of the valve demonstrated the infectious endocarditis. Immunosuppressive therapy was stopped. Vasculitis didn't recur. [Discussion] When encountering ANCA positivity in patients suspected of having systemic vasculitis, physicians should take appropriate steps to rule out infectious diseases, including CNE.

## P2-188

### A case of childhood-onset ANCA-negative eosinophilic granulomatosis with polyangiitis. successfully treated with mycophenolate mofetil combined with glucocorticoid

Norio Nakagawa, Kazutaka Ouchi, Shinji Akioka  
Department of Pediatrics, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: None

Eosinophilic granulomatosis with polyangiitis (EGPA) is a multisystem disorder characterized by chronic rhinosinusitis, asthma, and prominent peripheral blood eosinophilia. Mortality of childhood-onset EGPA is higher than that of adult-onset. We presented a case of childhood-onset EGPA treated with mycophenolate mofetil (MMF) that enabled to taper the required dose of glucocorticoid (GC) for keeping remission. A 10-year-old girl referred to our hospital due to eosinophilia. She had been medicated with anti-allergic drugs including leukotriene receptor antagonists for years as atopic dermatitis, asthma and allergic rhinitis. Several examinations revealed a lung nodule on X-ray, sinusitis, histological necrotizing vasculitis with eosinophilic infiltration in dermis and myocardial perfusion defect on scintigraphy. She was diagnosed as ANCA-negative EGPA. Remission was initially achieved with high dose GC, but it was unable to keep it without moderate and higher dosage of GC. MMF, not mizoribine, was successfully administered for maintenance of disease remission, which enabled to reduce the dosage of GC to minimum. MMF might be a potent immunosuppressant for maintaining remission along with steroid reduction in systemic vasculitides such as EGPA.

## P2-189

### Clinical features of relapsing patients with microscopic polyangiitis

Hideyuki Shiba<sup>1</sup>, Takeshi Shoda<sup>1</sup>, Takuro Ozaki<sup>1,2</sup>, Koji Nagai<sup>1,3</sup>, Shuzo Yoshida<sup>1</sup>, Takuya Kotani<sup>1</sup>, Tohru Takeuchi<sup>1</sup>, Shigeki Makino<sup>1</sup>, Toshiaki Hanafusa<sup>1</sup>

<sup>1</sup>First Department of Internal Medicine, Osaka Medical College Hospital, Takatsuki, Osaka, <sup>2</sup>Department of Internal Medicine, Arisawa General Hospital, Hirakata, Osaka, <sup>3</sup>Department of Internal Medicine, Koshokai Aino Hospital, Ibaraki, Osaka

Conflict of interest: None

[Objective] To assess the factors related the recurrence of microscopic polyangiitis (MPA) based on the clinical features. [Patients and Methods] We investigated 43 patients with MPA received the induction therapy for remission from Jan.2005 to Oct.2014 and analyzed the relevance between the clinical factors and the prognosis by Cox regression and log-rank test. [Results] 43 patients (20 males and 23 females) were investigated. Their average age and BVAS were 68.5 yrs and 15.7 points respectively. 36 patients maintained the remission and 7 patients relapsed. We analyzed the following factors by multivariate analysis, platelet number and total protein level at the remission, BVAS, steroid pulse therapy, IP, and GH. IP ( $p=0.0095^*$ ) and GH ( $p=0.0107^*$ ) were extracted for the significant factors. The hazard ratio of the recurrence was 7.44times at IP and 14.8times at GH, respectively. The cumulative remission rate was significantly lower in group of the interstitial pneumonia (IP) ( $p=0.0297^*$ ) and group of gastrointestinal hemorrhage (GH) ( $p=0.0005^*$ ). [Conclusion] It is needed to pay attention to the recurrence in MPA patients with IP and GH.

## P2-190

### The relapse and maintenance therapy in patients with Microscopic polyangiitis

Ryota Okazaki<sup>1</sup>, Yuriko Sueda<sup>2</sup>, Miki Takata<sup>1</sup>, Yasuyuki Hasegawa<sup>1</sup>, Akira Yamasaki<sup>1</sup>, Eiji Shimizu<sup>1</sup>

<sup>1</sup>Division of Medical Oncology and Molecular Respiriology, Tottori University Faculty of Medicine, <sup>2</sup>Tottori Prefectural Central Hospital

Conflict of interest: None

[Object] To assess the relation between the maintenance therapy and relapse in patients with microscopic polyangiitis (MPA). [Methods] We analyzed retrospectively 41 patients (18 males and 23 females) with MPA according to the Watts' algorithm from 2004 to 2014 at our hospital. [Results] The mean age of patients was 74.8 year-old. As maintenance therapy, 34 cases were treated with glucocorticoids (GC) alone, and 7 cases with immunosuppressive drug combination (azathioprine: 3 cases, oral cyclophosphamide: 2 cases, cyclosporin: 1 case, and tacrolimus: 1 case). Relapse occurred in 12 cases (29.2%), treated with maintenance GC therapy. Relapse symptoms were alveolar hemorrhage 3 cases, visual impairment 3 cases, renal dysfunction 2 cases, system symptoms 2 cases, peripheral neuropathy 1 case, gastrointestinal perforation 1 cases. Four patients died because of relapse. [Conclusion] All cases with MPA relapse had been treated with GC alone as maintenance therapy. To prevent MPA relapse is likely to require immunosuppressive drug combination as maintenance therapy.

## P2-191

### Two patients with microscopic polyangiitis who were withdrawn hemodialysis by glucocorticoid and rituximab therapy

Shoichi Sasaki<sup>1</sup>, Kaichi Kaneko<sup>1,2</sup>, Shinichi Kawai<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Ashikaga Red Cross Hospital, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Toho University School of Medicine

Conflict of interest: None

[Case 1] A 69-year-old male patient visited to our hospital with chest pain. Laboratory test showed elevated serum creatinine up to 6.30mg/dl and positive MPO-ANCA (288EU). Chest x-ray showed nodular lung lesion and renal biopsy showed crescentic glomerulonephritis (GN). He was diagnosed as rapidly progressive GN (RPGN) secondary to micro-

scopic polyangiitis (MPA). Hemodialysis and 60mg daily prednisolone (PSL) were started and followed by 375mg/m<sup>2</sup>/wk rituximab (RTX). He was withdrawn dialysis at 10th day. [Case 2] A 73-year-old male showed fever, eye discharge, and systemic edema. Laboratory test showed elevated serum creatinine up to 7.45mg/dl, CRP 11.86mg/dl, and positive MPO-ANCA (75EU). Renal biopsy showed crescentic GN, then he was diagnosed as RPGN secondary to MPA. Hemodialysis, glucocorticoid semi-pulse therapy followed by 40mg/day PSL and RTX of 375mg/m<sup>2</sup>/wk were started. He was withdrawn dialysis at the 10th day. Post-treatment renal biopsy showed intact remaining glomeruli. [Conclusion] It is suggested that RTX might be effective for withdrawal of hemodialysis in 2 patients with MPA.

## P2-192

### A case of sarcoidosis with suspected microscopic polyangiitis

Makoto Inoue  
Inoue Hospital

Conflict of interest: None

We present herein a rare case of sarcoidosis with microscopic polyangiitis and review the related literature. She experienced persistent pyrexia from March 2013. Positron emission tomography in August 2013 revealed bilateral hilar lymphadenopathy and increased fluorodeoxyglucose uptake. Elevated soluble interleukin-2 receptor levels and splenomegaly were also observed and she was referred to our institution on suspicion of lymphoma. Mediastinal lymph node biopsy resulted in a diagnosis of sarcoidosis. During the course of treatment, she developed concomitant alveolar hemorrhage. Furthermore, myeloperoxidase antineutrophil cytoplasmic antibodies and elevated inflammatory response were detected on blood testing and occult blood and uric protein were found on urinalysis. In addition to these and physical findings, mononeuropathy multiplex was also observed. Pathology, physical and blood test findings led to a diagnosis of sarcoidosis with microscopic polyangiitis. Although alveolar hemorrhage has also been reported in uncomplicated sarcoidosis, a favorable prognosis can usually be achieved with prednisolone monotherapy. However, microscopic polyangiitis often has a poor prognosis.

## P2-193

### A case of relapsing microscopic polyangitis with active pulmonary tuberculosis

Koichi Sumida<sup>1</sup>, Koji Harada<sup>1</sup>, Juri Tsukahara<sup>1</sup>, Yuto Kasahara<sup>1</sup>, Yukinari Yamaguchi<sup>1</sup>, Yasuhiro Akai<sup>2</sup>

<sup>1</sup>Department of Nephrology and Rheumatology, Rakuwakai-Otowa Hospital, <sup>2</sup>Center for Rheumatic Diseases, Nara Medical University Hospital

Conflict of interest: None

**Case report:** 66 year-old man was admitted for rapid deterioration of renal function. Laboratory data showed massive proteinuria, gross hematuria, and elevation of MPO-ANCA (155 EU). Because renal biopsy revealed necrotizing crescentic glomerulonephritis, he was diagnosed as microscopic polyangitis. Despite the presence of pleural calcification, bronchiectasis and positive of interferon- $\gamma$  release assay, M.tuberculosis was not detected. He was thought to be the latent tuberculosis. Prednisolone (PSL) 40 mg/day with prophylactic isoniazid 300 mg/day was started with satisfactory improvement of renal function, and PSL was tapered to 20 mg/day for 2 months. Six months after the initiation of corticosteroid he complained of dyspnea on effort. Since M.tuberculosis was cultured from the sputum, he was diagnosed as pulmonary tuberculosis. The administration of rifampicin, pyrazinamide, and levofloxacin was started and PSL was reduced to 10 mg/day. Three months after the treatment persistent fever and fatigue developed. Because of the elevation of CRP and MPO-ANCA, he was confirmed to be a relapse of MPA. **Summary:** There are various problems for the treatment of MPA in the patients with tuberculosis. We report this case with literature review for the management of MPA with tuberculosis.

## P2-194

### Tocilizumab may be effective for remission induction of rheumatoid arthritis complicated with ANCA-associated vasculitis

Koji Nishimura, Michihito Sato, Kazutoshi Aoki  
JCHO Saitama Medical Center

Conflict of interest: None

[Case] An eighty-eight-year-old male was admitted to our hospital because of lower leg edema, arthralgia, paresthesia and hematuria. A physical examination disclosed swollen and tender joints of both 2-5 MCPs, hands and elbows. Both lower thighs were edematous with paresthesia. Fine crackles were auscultated in the back. Urinalysis showed urine occult blood 3+ over, granular-cast > 30 / w. Serum creatinine was 1.45 mg/dl, CRP 9.38 mg/dl, ESR 130 mm/h, ACPA <0.6u/ml, RF 73 u/ml, and MPO-ANCA >300 u/ml. Chest computed tomography revealed interstitial pneumonia. Therefore this patient was diagnosed as rheumatoid arthritis complicated with ANCA-associated vasculitis. Methyl prednisolone 500 mg for 3 days and PSL 60 mg/day was administered. Physical and laboratory findings improved promptly. On the 8th day, tocilizumab (162 mg) was injected subcutaneously. Prednisolone was decreased to 20 mg/day in three weeks without complications or exacerbation. [Clinical meaning] In treatment of ANCA-associated vasculitis, rapid reduction of the amount of steroid became possible by combined use of IVCY or rituximab. However, complications in the old weak patients are still serious problems. Combined use of tocilizumab may be the more secure choice of the treatment of ANCA-associated vasculitis.

## P2-195

### A case of IgA vasculitis with onset of polymyalgia rheumatica like symptom

Hiroyuki Honoki, Satoshi Yamaguchi, Atsushi Matsui, Maiko Obi, Reina Tsuda, Koichiro Shinoda, Hirofumi Taki, Kazuyuki Tobe  
First Department of Internal Medicine, University of Toyama, Japan

Conflict of interest: None

A 63 year old man was suffered from of myalgia from bilateral neck to upper limbs. Polymyalgia rheumatic was diagnosed and PSL 15mg per day was started. His symptom did not improved and admitted our hospital. physical findings showed palpable Purpura in bilateral lower limbs. Skin biopsy showed vasculitis with IgA and C3 deposit. IgA vasculitis was diagnosed. High dose of PSL improved his symptom.

## P2-196

### Risk factors for poor prognosis of IgA vasculitis

Taro Horino, Tatsuki Matsumoto, Kazu Ode, Koji Ogata, Yoshiko Shimamura, Kosuke Inoue, Yoshinori Taniguchi, Yoshio Terada  
Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi University

Conflict of interest: None

[Objectives] Our goal is to detect risk factors for prognosis of IgA vasculitis. [Methods] Seven IgA vasculitis patients who had been admitted to our hospital. All patients were proven as IgA vasculitis by pathohistological examinations. We classified three gropes; sgood responder (group A) and poor responder (group B). We assess the correlation between renal prognosis and laboratory data. [Results] Female were 4 (57.1%). Renal biopsy was performed in 4 patients, and skin biopsy was in 3. Group A and B included 4 and 3 patients, respectively. The average length of stay of group A was 33.2 days, and group B was 316. Patients in both groups needed to treat with mPSL pulse therapy following oral PSL for a while. Date showed that poor prognosis might be associated with low level of Alb or Plt, massive proteinuria, and positive occult blood test in the stool. [Conclusion] Our date suggests that in IgA vasculitis patients with nephritis, poor prognosis could be associated with other organ damage, including intestinal disturbance, and hematopoietic damage.

## P2-197

### A case of multiple myeloma complicated with cryoglobulinemic vasculitis

Takakazu Hasegawa<sup>1</sup>, Masaki Okazaki<sup>2</sup>, Kumiko Umemura<sup>1</sup>, Michita Suzuki<sup>1</sup>, Kyoko Takano<sup>1</sup>, Eiji Nagasawa<sup>1,4</sup>, Nobuyoshi Minemura<sup>1,3</sup>, Masao Katayama<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, National Hospital Organization Nagoya Medical Center, Nagoya, Japan, <sup>2</sup>Department of Nephrology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan, <sup>3</sup>Department of Internal Medicine, Tamazensyoen, National Sanatorium, Tokyo, Japan, <sup>4</sup>Nagasawa Clinic, Nagoya, Japan

Conflict of interest: None

This is a case of a 47-year-old man developed talalgia over the course of about 2 months and did not improve despite analgesics. Then purpura on his lower legs and fever appeared. At the presentation to our hospital, his serum IgG, C-reactive proteins and creatinine were elevated. Within several days after presentation, his serum creatinine was more elevated. Vasculitis was doubted from pathological findings of skin biopsy, but ANA and ANCA were negative. After admission oral prednisolone and cyclophosphamide therapy started. But his renal function did not improve despite this therapy, so hemodialysis, mPSL pulse and plasma exchange were administered. He had M-protein, so he was diagnosed with MGUS based on the results of a bone marrow aspiration. Renal biopsy doesn't showed myeloma kidney or ANCA-associated vasculitis findings. And his cryoglobulin test was positive, so the cause of his purpura and renal failure was cryoglobulinemic vasculitis. His renal function improved following therapy, and he discharged. But after about 2 months his serum creatinine were elevated. After readmission, he was diagnosed with multiple myeloma (symptomatic) based on the results of a bone marrow aspiration. We present a case of multiple myeloma complicated with cryoglobulinemic vasculitis that developed renal failure.

## P2-198

### A case of unclassifiable systemic vasculitis (ANCA-negative small vessel vasculitis)

Eri Sugano, Yuko Okamoto, Tsuyoshi Kobashigawa, Hikota Osawa, Masanori Hanaoka, Daisuke Hoshi, Hisae Ichida, Yasuhiro Katsumata, Yasushi Kawaguchi, Hisashi Yamanaka  
Institute of Rheumatology Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Case] 40 year-old female [Chief complaint] seizure [Medical history] 1.5 years before the admission, the patient noticed finger erythema. After, sudden visual loss developed, which was retinal vasculitis. 30 mg predonine was administered and tapered. Erythema revealed leucocytoclastic vasculitis. 3 months before, the retinal vasculitis relapsed with fever and weight loss. FDG-PET/CT showed generalized lymphadenopathy. She was taken by ambulance with generalized seizure. MRI (T2WI) showed high signal at both basal ganglia, and cerebral small vessel vasculitis was suspected by perfusion images. Lymph node revealed necrotizing lymphadenopathy. Serologic testing, anti-centromere antibody was positive but ANCA was negative. The diagnosis was unknown but we considered a series of history as systemic vasculitis and high dose predonine and cyclophosphamide pulse therapy were administered. [Clinical importance] This case is not classifiable by the CHCC2012. Systemic small vessel vasculitis without granuloma seems like ANCA negative MPA. RemIT-JAV says 1/78 patient of MPA shows negative ANCA result, and 2/31 patients of unclassified AAV show negative ANCA. This case never showed specific organ disease. It is important to accumulate unclassified case to progress the diagnose of vasculitis.

## P2-199

### An Autopsy Case of MPO-ANCA Positive Microscopic Polyangiitis with Intracerebral Hemorrhage

Yoshia Miyawaki<sup>1</sup>, Ken-ei Sada<sup>1</sup>, Keiji Ohashi<sup>1</sup>, Michiko Morishita<sup>1</sup>, Takayuki Katsuyama<sup>1</sup>, Eri Katsuyama<sup>1</sup>, Haruki Watanabe<sup>1</sup>, Mariko Narazaki<sup>1</sup>, Noriko Toyota Tatebe<sup>1</sup>, Koichi Sugiyama<sup>1</sup>, Katsue Sunahori

Watanabe<sup>1</sup>, Hiroshi Wakabayashi<sup>1</sup>, Tomoko Kawabata<sup>1</sup>, Jun Wada<sup>1</sup>, Hirofumi Makino<sup>2</sup>

<sup>1</sup>Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine Dentistry and Pharmaceutical Sciences, Okayama, Japan, <sup>2</sup>Okayama University Hospital, Okayama, Japan

Conflict of interest: None

A 77-year-old man was admitted to local hospital because of high fever, elevated serum C-reactive protein (CRP) level, and dysuria. Because of MPO-ANCA positive, he referred to our hospital. On admission, laboratory findings were follows: MPO-ANCA, 128.0 IU/mL; serum creatinine, 1.67 mg/dL; CRP, 21.5 mg/dL. Finally he was diagnosed with microscopic polyangiitis (MPA) and started administration of glucocorticoids concomitant with intravenous cyclophosphamide. His general symptoms improved in the short term. On day 12, he complained headache and lost consciousness. A head CT scan showed an acute lesion of intracerebral hemorrhage. Emergent evacuation was performed but he passed away on day 14. The autopsy revealed vasculitis of the small to middle vessels in liver, heart, small intestine, rectum, gallbladder, bronchus, prostate, and testis. Neuropathological findings revealed cerebral hemorrhage of thalamus, cerebellum, and brainstem caused by necrotizing vasculitis. Cerebral vasculitis is difficult to be confirmed histologically but is associated with poor prognosis. Therefore we should determine treatment strategy based on a substantial assessment including central nerve system.

## P2-200

### A case of microscopic polyangiitis associated with cerebral aneurysms and brainstem lesions

Ryota Ozawa, Naoki Ezawa, Kenichi Hoshi, Hiroyuki Yahikozawa  
Neurology, Nagano Red Cross Hospital, Nagano, Japan

Conflict of interest: None

A 57-year-old man complained of diplopia. The brain MRI showed a T2 high-signal lesion in the midbrain. Furthermore aneurysms in the anterior communicating and right middle cerebral arteries were found and clipping was performed. The patient developed myalgia and numbness in fingers and feet after 5 months. The brain MRI revealed a new lesion in the left pontine tegmentum. The blood and urine tests showed rapidly progressive glomerulonephritis with a marked inflammatory response. Mononeuritis multiplex was confirmed by a nerve conduction study. The patient was finally diagnosed with microscopic polyangiitis (MPA) because of the positive serum MPO-ANCA as well as the vasculitis found by the skin biopsy. After treatment with corticosteroid, the symptoms and renal dysfunction improved, and inflammation controlled. The pathological findings of cerebral aneurysms were consistent with the chronic phase of vasculitis as inflammatory cell infiltration mainly consisting of plasma and lymphoid cells occurred in the vessel wall. We concluded the aneurysms were caused by MPA. Only a limited number of reports of aneurysm associated with MPA have previously been published, and one of which was a cerebral aneurysm case. Particular attention must be paid to this rare complication caused by MPA.

## P2-201

### Granulomatosis with polyangiitis presenting with dysphagia as cranial neuropathy

Lisa Kosuge<sup>1</sup>, Kenichiro Tokunaga<sup>2</sup>, Naoho Takizawa<sup>2</sup>, Masahiro Minoda<sup>2</sup>, Hideto Oshikawa<sup>2</sup>, Kazuo Matsui<sup>2</sup>

<sup>1</sup>Department of General Internal Medicine, Kameda Medical Center, <sup>2</sup>Department of Rheumatology, Kameda Medical Center, <sup>3</sup>Department of General Internal Medicine, Awa Regional Medical Center

Conflict of interest: None

Granulomatosis with polyangiitis (GPA) is a systemic vasculitis affecting small vessels. While neurological involvement is common, cranial nerve involvement is less frequent. We report the case of a 66-year-old man who presented dysphagia as cranial neuropathy. He had chronic cough from 2 years ago, left hearing loss and polydipsia polyuria from 4 months ago. Two months earlier, he was diagnosed with organizing pneu-

monia by lung infiltrates, and prednisolone was administered. He was also pointed out diabetes insipidus and pituitary gland enlargement on MRI. During steroid tapering, his voice got smaller and he had persistent fever. On admission to our department, he presented rhinolalia aperta and dysphagia. There were conjunctival injection, right nasal bleeding, left soft palatal paralysis and right drop foot. The lab showed inflammatory reaction, renal failure and proteinuria. ANCA was negative. Brain MRI didn't show new findings. Cerebral fluid tests revealed discrepancy between protein level and cell counts. With these results, we strongly suspected cranial neuropathy by GPA caused his dysphagia. Steroid pulse therapy and IVCYC were immediately started, and his symptoms improved soon after the therapy. Finally, the lung and renal pathology showed glomerulomatous vasculitis.

## P2-202

### **A case of eosinophilic granulomatosis with polyangiitis (EGPA) complicated with subarachnoid and subdual hemorrhage**

Yukimi Otsuka<sup>1</sup>, Atsushi Tanaka<sup>1</sup>, Yojiro Arinobu<sup>1</sup>, Shotaro Kawano<sup>1</sup>, Aya Koto<sup>1</sup>, Hiroki Mitoma<sup>1</sup>, Mitsuteru Akahoshi<sup>1</sup>, Hiroaki Niino<sup>2</sup>, Hiroshi Tsukamoto<sup>1</sup>, Koichi Akashi<sup>1</sup>

<sup>1</sup>Department of Clinical Immunology, Rheumatology, and Infectious Diseases, Kyushu University Hospital, <sup>2</sup>Department of Clinical Education Center, Kyushu University Hospital

Conflict of interest: None

A 46-year-old female with histories of asthma and sinusitis was admitted to our hospital with complaints of fever, mononeuritis multiplex and purpura. Laboratory tests showed increased eosinophil count (5020 /  $\mu$ l), CRP (3.2 mg/dl), MPO-ANCA (169.6 U/ml) and urinary abnormalities (proteinuria, occult blood and granular cast). Skin biopsy revealed fibrinoid necrosis of the arteries with infiltration of eosinophils around them. Overall, diagnosis of EGPA was made. Before induction therapy, she exhibited sudden onset of headache. Findings on brain MRI revealed subarachnoid and subdual hemorrhage. PSL 1mg/kg was started and IVCY was added. Then, headache and findings on brain image improved. Despite being rare, subarachnoid and subdual hemorrhage can be presenting features of vasculitis associated with EGPA. Since cerebral involvement could be a major cause of morbidity and mortality, we should consider conducting brain image examination when patients exhibit sudden headache and/or paralysis. In those cases, immunosuppressive therapy could be effective.

## P2-203

### **Eosinophilic granulomatosis with polyangiitis and multiple cerebral infarction**

Marina Hamaguchi, Yosuke Nagasawa, Kaita Sugiyama, Atsuma Nishiwaki, Natsumi Ikumi, Takamasa Nozaki, Hirotake Inomata, Hiromi Karasawa, Hidetaka Shiraiwa, Mitsuhiro Iwata, Hitomi Haraoka, Noboru Kitamura, Yoshihiro Matsukawa, Masami Takei

Division of Hematology and Rheumatology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

Conflict of interest: Yes

The patient is a 68-year-old woman. She presented to her local clinic with weakness of both upper limbs and numbness in the beginning of May in 2014. Furthermore, she also noticed exanthemata in both lower limbs. She was followed-up by being on vasodilating drugs and an ointment. But exanthemata still spread in her oral cavity. Numbness had gradually progressed and ended up not being able to walk which made her call for an ambulance. Besides a 10-year history of asthma, her past medical history is insignificant. Physical examination was significant for weakness of both upper limbs, numbness and abnormal reflexes. The laboratory studies were also notable for elevation of eosinophile. A MRI revealed clustered acute ischemic changes in the both side of cerebral hemispheres. She was diagnosed with eosinophilic granulomatosis with polyangiitis and mononeuritis multiplex and multiple cerebral infarction caused by polyangiitis. Since the progression of neurological damages was rapidly, she started to be on steroid pulse therapy on the day of admission. She also started to be on 160 milligrams per day of Ozagrel sodium and 400 milligrams per day of concentrated glycerin for multiple

cerebral infarction as well. Therefore, neurological findings have improved.

## P2-204

### **A case of otitis media with ANCA associated vasculitis(OMAAV) with hearing loss and dizziness**

Maiko Obi<sup>1</sup>, Hiroyuki Honoki<sup>1</sup>, Satoshi Yamaguchi<sup>1</sup>, Atsushi Matsui<sup>1</sup>, Reina Tsuda<sup>1</sup>, Koichiro Shinoda<sup>1</sup>, Hirofumi Taki<sup>1,2</sup>, Kazuyuki Tobe<sup>1,2</sup>

<sup>1</sup>First Department of Internal Medicine, Hospital of University of Toyama, <sup>2</sup>First Department of Internal Medicine, University of Toyama

Conflict of interest: None

**【Case】** A 74-year-old woman complained of hearing loss and dizziness for 6 months. She also complained of fever, headache and neck pain. She was diagnosed as polymyalgia rheumatica and treatment with PSL (20mg, once daily) improved her hearing loss and neck pain, however fever and headache sustained. She was suspected to have ANCA associated vasculitis (AAV) because of MPO-ANCA positivity. On admission she was febrile, however, she had become afebrile and headache disappeared after we changed the prescription of PSL from once daily (20-0-0) to twice daily (10-0-10). Temporal bone CT did not reveal a soft tissue density at both mastoid and middle ear cavities, however, we considered her otological symptoms suggesting labyrinthitis caused by AAV and diagnosed her otitis media with AAV (OMAAV) based on the revised version of diagnostic criteria of OMAAV in Japan. **【Clinical Importance】** Recently, otological symptoms have been reported in AAV cases. And proposal of the new clinical entity called OMAAV was discussed in Japan. The early diagnosis of OMAAV is very important not only to reverse sensorineural hearing loss but to prevent the development of systemic vasculitis which is high mortality. We discuss clinical features of OMAAV with our previous experienced 5 cases of OMAAV.

## P2-205

### **A case of microscopic polyangiitis (MPA) complicated with multiple cerebral bleedings caused deafness**

Makoto Oishi<sup>1</sup>, Ayako Nishino<sup>1</sup>, Shin-ya Kawashiri<sup>1,2</sup>, Sosuke Tsuji<sup>1</sup>, Masataka Umeda<sup>1</sup>, Shoichi Fukui<sup>1</sup>, Takahisa Suzuki<sup>1</sup>, Yoshikazu Nakashima<sup>1</sup>, Yoshiro Horai<sup>1</sup>, Yasuko Hirai<sup>1</sup>, Tomohiro Koga<sup>1</sup>, Naoki Iwamoto<sup>1</sup>, Kunihiko Ichinose<sup>1</sup>, Mami Tamai<sup>1</sup>, Hideki Nakamura<sup>1</sup>, Tomoki Origuchi<sup>3</sup>, Atsushi Kawakami<sup>1</sup>

<sup>1</sup>Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, <sup>2</sup>Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, <sup>3</sup>Department of Rehabilitation Sciences, Nagasaki University Graduate School of Biomedical Sciences

Conflict of interest: None

A 80-years-old woman visited to our hospital for sudden hearing loss in May 2014. She was diagnosed as sudden deafness, and treated with prednisolone (PSL). However, her deafness had slightly improved. On laboratory data, CRP elevated to 5.69 mg/dl and MPO-ANCA was positive. Hematuria and proteinuria were detected. Brain magnetic resonance imaging revealed findings of multiple cerebral microbleedings and high intensity of left cochlear. She was diagnosed as microscopic polyangiitis (MPA) complicated with cerebral microbleedings, glomerulonephritis and internal otitis. She was treated with methylprednisolone pulse therapy (500mg daily, 3 days) and following oral PSL 30mg daily. Although CRP, hematuria and proteinuria have improved, no improvement of deafness was observed. We report here a rare case of MPA complicated with multiple cerebral microbleeds, which are suggested to cause deafness.

## P2-206

### **IgG4-related sclerosing cholangitis (IgG4-RSC) diagnosed by obstructive jaundice during remission of various autoimmune diseases: A case report**

Kosuke Doi, Kazuhiro Hatta, Hiroyasu Ishimaru, Teruhisa Azuma, Shuko Hashimoto

Tenri Hospital, Nara, Japan

Conflict of interest: None

**[Case]** A 66-year-old Japanese man was diagnosed as having an autoimmune hepatitis and a pure red-cell aplasia 5 years ago, and idiopathic thrombocytopenic purpura 4 years ago as well. We also detected high value of IgG4 and hypocomplementemia, which was difficult to make sense. However we successfully treated them with prednisolone (PSL) and cyclosporine A (CyA). Then he attained remission and PSL and CyA was reduced to 5mg/day and 150mg/day, respectively. One month before admission, increase in biliary enzymes and thickening of bile duct wall by contrast-enhanced CT were detected. High level of IgG4 and diffuse stricture at bile duct of hepatic portal region by MRCP and ERCP were also pointed out. Specimens from biopsy of gallduct revealed invasion of inflammatory cells, consisting of mainly plasmacytes with 20 to 30% of IgG4-positive ones and lymphocytes under epithelium. After ruling out of malignancy by cytology, we diagnosed him as IgG4-RSC on the grounds of these findings, beginning to treat him by PSL 45mg/day. **[Discussion]** It is considered to be rare that IgG4-RSC isn't associated with AIP. The case wasn't associated with AIP but with various autoimmune diseases which are unknown about the relationship to IgG4-RSC. We will discuss the issues using literature review.

## P2-207

### A case of IgG4 related disease with pancytopenia

Tsuneo Sasai, Kazuhiro Hatta, Hiroyasu Ishimaru, Teruhisa Azuma, Shuko Hashimoto  
Tenri Yorodu Hospital

Conflict of interest: None

IgG4 related disease influence various organs. We report a case of IgG4 related disease with pancytopenia. A 75-year-old man visited the Dermatologist with leg skin rash. After skin biopsy, he was treated with steroid preparation. Then, skin rash disappeared, but the result of the biopsy showed the perivascular neutrophilic infiltration. For further examination of collagen disease, he was introduced our department. He has no symptoms, but bilateral submandibular enlargement, bilateral cervical, axillary, and inguinal lymph node enlargement. Laboratory study showed pancytopenia, ANA: 160, hypocomplementemia, and high IgG4 (IgG4: 270mg/dl). He was not fully classified to have SLE with these signs and data. A CT and FDG-PET scan showed bilateral cervical, mediastinal, axillary, and inguinal lymph node enlargement. The result of the cervical lymph node biopsy showed IgG4 related disease (IgG4+/IgG<40%, but the count of IgG4+/HPF >10). To detect the cause of pancytopenia, we did bone marrow aspiration and biopsy, which showed no evidence of malignancy. So we concluded IgG4 related disease with pancytopenia, and observed him without treatment. IgG4 related disease influence various organs, but concomitant pancytopenia is rare, so we report the case with bibliographical consideration.

## P2-208

### A case of IgG4 related disease with severe Raynaud's phenomenon and jaw claudication

Yasushi Mizuno, Yumi Sono, Yohei Kanzawa, Hayato Shimizu, Hiroaki Nishioka  
Department of General Internal Medicine, Kobe City Medical Center General Hospital, Kobe, Japan

Conflict of interest: None

A 55-year-old man was admitted to our department with lymph nodes swelling and Raynaud's phenomenon. He had past history of chronic sinusitis and bronchial asthma. He felt worsening of his sinusitis 4 months before admission and facial edema 3 months before. His blood test revealed elevated CRP and serum IgG4. Submandibular gland and axillary lymph node biopsy showed many IgG4 positive plasma cells. We diagnosed him as IgG4 related disease and started prednisolone (PSL) 40mg/day. His facial swelling and nasal obstruction was improved, but Raynaud's phenomenon got worse and his fingers became gangrenous. We started to prescribe sildenafil, which made his symptoms better. Jaw claudication and swelling of temporal arteries were appeared 3 months after starting PSL. Ultrasound revealed occlusion of superficial temporal ar-

tery. Temporal artery biopsy disclosed fibrosis and infiltration of plasma cells, but IgG4 positive cells were not predominant. We performed CT and MRI, which did not show large vessel vasculitis. His jaw claudication was disappeared after treatment with 40mg PSL and methotrexate. Although temporal artery biopsy did not show characteristic findings of IgG4 related disease, his Raynaud's phenomenon and jaw claudication suggest involvement of small arteries.

## P2-209

### A case of IgG4RD at first suspected of CTD, but lymph node swelling developed afterwards, ML became one of the differential diagnosis with chromosomal abnormality

Kazuhiro Hatta, Teruhisa Azuma, Hiroyasu Ishimaru  
Department of General Internal Medicine, Tenri Hospital, Tenri, Japan

Conflict of interest: None

A 54 year-old male was admitted to our hospital, he had been well until before he complaint arthralgia and bilateral hand edema two years before admission. He was referred to our hospital for further exam for collagen disease, where positive ANA, DNA Ab was shown. Adding arthralgia to these Lab date, SLE was suspected but not fully diagnostic. These symptom disappeared spontaneously. But two months before admission, he noticed inguinal pain and CT revealed lymphadenopathy. He referred to hematologist in our hospital, where IgG4 elevation were shown, he again transferred to our ward. LD showed IgG4 (228) IL2R (2122) both elevation, but PSA was normal. Renal biopsy and prostatic biopsy was done, and both results were compatible with IgG4RD except for presence of prostatic cancer. So inguinal lymph node biopsy was done for ruling out of ML, but definite chromosomal abnormality was shown, and there again possibility of ML became elevated. We afterward closely observed the his clinical course, Gradually IgG4 level decreased and lymphadenopathy disappeared completely on FDG-PET examination. **[Conclusion]** This case was very suggestive for the understanding of pathophysiology of this disease.

## P2-210

### A natural clinical course of IgG4-related disease for about 30 years

Yuichi Torisu<sup>1</sup>, Nozomi Iwanaga<sup>1</sup>, Yasumori Izumi<sup>1</sup>, Taiichiro Miyashita<sup>4</sup>, Kiyoshi Migita<sup>5</sup>, Atsushi Kawakami<sup>6</sup>

<sup>1</sup>National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan, <sup>2</sup>National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan, <sup>3</sup>National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan, <sup>4</sup>Miyashita Rheumatology Clinic, <sup>5</sup>National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan, <sup>6</sup>Nagasaki University Graduate School of biomedical Sciences

Conflict of interest: None

A case is a 75-year old man. He presented with submandibular lymph node swelling in 1984. Malignant lymphoma was suspected, but lymph node biopsy showed no malignancy cells. In 1998, mediastinal lymphadenopathy and tumors of the left renal pelvis and the retroperitoneum were detected by CT scan. Several examinations didn't lead to a definite diagnosis. The lymph node gradually grew on CT for several years. In 2007, kidney biopsy showed the infiltrates of plasma cells which were negative for IgG4. In 2009, he had a TUR-P surgery for benign prostatic hypertrophy. IgG 4-positive plasma cell infiltration was detected in prostatic tissue. In August of 2014, he was admitted to our hospital for the evaluation of progressive mediastinal lymphadenopathy. Lymph node biopsy showed IgG4-positive plasma cell infiltration (IgG4/IgG>80%). Serum level of IgG4 was elevated. Because of these findings, he was diagnosed with IgG4-RD. He received PSL30mg and mediastinal lymphadenopathy and tumors of the left renal pelvis and the retroperitoneum reduced markedly. IgG4-RD is a new disease concept. Its prognosis of long time was not known. We report this case because we could observe its natural clinical course for about 30 years.

## P2-211

### A case of IgG4-related disease with mesenteric panniculitis

Makiko Yashiro, Shuzo Sato, Naoki Matsuoka, Tomoyuki Asano, Hiroko

Conflict of interest: None

A 69-year-old man suffered from high fever, arthralgia and fatigue. The physical findings revealed bilateral inguinal lymphadenopathy. His laboratory data showed high white blood cell and eosinophil counts (20,000 / $\mu$ L and 13,000 / $\mu$ L, respectively). The serum creatinine level was elevated to 1.33 mg/dL. Urinalysis showed hematuria. Abdominal computed tomography (CT) demonstrated intraperitoneal and inguinal lymphadenopathy with elevated contrast enhancement of the mesentery of small intestine (misty mesentery). T2 weighted MRI also showed intense signal of the mesentery. Inguinal lymph node biopsy was performed. Microscopic examination revealed intense IgG4-positive plasma cell infiltration and the IgG4/IgG ratio was 50%. The serum level of IgG4 was elevated to 768 mg/dl. He was given a diagnosis of IgG4-related disease with mesenteric panniculitis. Oral prednisolone at an initial dose of 40mg/day alleviated his symptoms, and laboratory data improved with the amelioration of CT findings. Only a few cases of IgG4-related sclerosing mesenteritis have been reported. This is the first case report to present mesenteric panniculitis in a patient with IgG4-related disease.

## P2-212

### A case of IgG4-related disease with pancytopenia

Akira Jibatake, Tamao Nakashita, Shinji Motojima  
Rheumatology and Allergy Department, Kamada Medical Center, Kamogawa, Chiba, Japan

Conflict of interest: None

[Objectives] The IgG4-related disease causes multiple organ dysfunction, and IgG4 positive plasma cell is known to be involved in the bone marrow. but no case of IgG4-related disease has been reported to be with pancytopenia before. [case] a 68-year-old male who presented to the local clinic with the chief complaint of dyspepsia persistent for one month in May, 2014. He was found to have pancytopenia, eosinophilia, hyperglobulinemia, interstitial lung disease on chest X-ray. Urine test was protein 1+, increased  $\beta$ 2MG. the laboratory test shows WBC 2500/ $\mu$ L (Eo 53%), Hb 9.7 g/dL, Plt 96,000/ $\mu$ L, TP8.2g/dl, Alb2.5g/dl, hypocomplementemia, ANA2560 (peripheral pattern), negative anti SS-A antibody, IgG 4,010mg/dl, IgG4 1,090 mg/dl, IgE376IU/ml. Chest CT showed combined pulmonary fibrosis and emphysema. storiform fibrosis and increased IgG4/IgG was found in renal tissue and made a final diagnosis of IgG4-related renal disease. PSL0.6mg/kg was begun and the hypocomplementemia and the high titer of IgG4 and IgG returned to normal value. [Conclusion] pancytopenia occurred in IgG4-related disease is rare but not none, sometimes bone marrow biopsy should be performed and evaluated with caution.

## P2-213

### Can Behçet's disease be cured? The clinical course of 100 patients

Mai Okubo<sup>1</sup>, Hirotohi Kikuchi<sup>1</sup>, Daisuke Tsukui<sup>1</sup>, Kurumi Asako<sup>1</sup>, Maki Takayama<sup>1</sup>, Akiko Okamoto<sup>1</sup>, Toshihiro Nanki<sup>2</sup>, Tamiko Yanagida<sup>1</sup>, Hajime Kono<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan, <sup>2</sup>Teikyo Academic Research Center, Teikyo University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Background] Natural history of Behçet's disease (BD) is not well documented and it is not known that when and how the remission happens in the course of disease. [Methods] We investigated the clinical course of each symptoms and prognosis of BD in 100 patients who currently visit our department. [Results] Of the 100 patients, 55% were male (age at diagnosis of BD 33.2 $\pm$ 9.1 years old) and 45% were female (38.3 $\pm$ 11.7); and HLA B-51 was positive in 57.1%. Frequency of stomatitis, genital ulcer, cutaneous lesions, and ocular lesions was 100%, 87%, 96%, and 59%, respectively. The most lasting disease is stomatitis as mean duration of around 30 years, and the remission rate was 28%. Eye

symptoms were noted in 59% of cases and 22 of the 118 eyes became blind. Frequency of vascular, intestinal, and CNS lesions was 20%, 22%, and 19%, respectively. Also remission rate was 15%, 9.1, and 47.4%, respectively. 20% of intestinal diseases required surgery. The prognosis of the acute type of CNS involvement is favorable and the remission rate was 100%, in contrast, the remission rate of the chronic progressive type of CNS was only 20%. [Conclusion] While stomatitis persecutes BD patients for long time, impairment was caused by ocular, vascular, intestinal or chronic progressive type of CNS disease.

## P2-214

### Radio-graphical findings of hand and wrist specific for arthritis in Behçet's disease

Satoko Tashiro<sup>1</sup>, Yukihide Ono<sup>1</sup>, Yukiko Tokuda<sup>1</sup>, Yuri Sadanaga<sup>1</sup>, Rie Suematsu<sup>1</sup>, Nobuyuki Ono<sup>1</sup>, Syuichi Koarada<sup>1</sup>, Akihide Ohta<sup>2</sup>, Yoshifumi Tada<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Saga University, Saga, Japan, <sup>2</sup>Division of Nursing, Saga University, Saga, Japan

Conflict of interest: None

[Objectives] In Behçet's disease (BD), it is believed that arthritis of hands are rare and reported cases with MRI findings of BD are also seldom. To study the imaging features of the hand and wrist in BD. [Methods] In total of 33 patients with BD, we studied six patients fulfilling the diagnostic criteria of BD, MRI findings of the hand and wrist arthritis. [Results] The patients were 37 to 65 years old, and the mean disease duration was 17.6 years. The mean duration of arthritic hand symptoms was 2.1 years. All patients demonstrated synovitis and erosive arthritis on MRI. None of them had bone marrow edema. Both rheumatoid factor and anti-CCP antibodies were negative. [Conclusion] Although erosive arthritis and synovitis of the fingers and wrists may occur frequently in BD, absence of bone marrow edema was found in BD patients. Further study should be required to differentiate findings specific for BD from other rheumatic diseases and syndrome.

## P2-215

### A pilot study of the eicosapentaenoic acid/arachidonic acid (EPA/AA) ratio level of Japanese patients with Behçet's disease

Tsuyoshi Kobashigawa, Yuki Nanke, Toru Yago, Hisashi Yamanaka, Shigeru Kotake  
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Objectives] To investigate the relationships between states of Behçet's disease (BD) and the transitions of fatty acid (eicosapentaenoic acid/arachidonic acid (EPA/AA) ratio) for the patients with BD. [Methods] We enrolled 25 patients with BD and analyzed their levels of EPA/AA ratio. The examinations of EPA/AA ratio were performed in a daily general blood survey. The disease activity was shown with the score of patient's global assessment VAS (PtGA), in this study. [Results] We analyzed 25 BD patients visited our clinic in recent 2 years: 2012 to 2013. The characteristics of 25 patients with BD (7 males) were as shown below: oral lesions were shown in all BD patients (100%), skin lesions: 96%, genital ulcers: 76%, ocular lesions: 40%, arthritis: 76%, intestinal lesions: 48%, neural lesions: 12%, vascular lesions: 20%. The total 75 times analyzed in the BD patients were divided into 3 categories: 19 were over the reference values (0.11 – 0.50), 54 within and 2 under and the mean EPA/AA ratio (SD) were 0.84 (0.29), 0.27 (0.097) and 0.077 (0.0011), respectively. The EPA/AA ratio levels were not decreased, which may not related to PtGA in 5 vascular-BD patients. [Conclusion] The EPA/AA ratio level were not related the activities in the Japanese BD patients.

## P2-216

### Clinical characteristics of Vasculo-Behçet's disease in our hospital

Makiko Higuchi, Tomoya Miyamura, Masataka Nakamura, Shoko Kodama, Soichiro Takahama, Yu Kaku, Rumi Minami, Masahiro Yamamoto, Eiichi Suematsu



Department of Internal Medicine and Rheumatology, Clinical Research Institute, National Hospital Organization, Kyushu Medical Center, Fukuoka, Japan

Conflict of interest: None

We investigated the clinical manifestation of nine Vasculo-Behçet's disease (BD) patients in our hospital. Six males and three females were involved, including seven with complete type, two with incomplete type. The patient's median ages were 43 years old, durations from initial manifestation to BD diagnosis were 1 months~5 years, and durations to vasculo-BD diagnosis were 1 months~10 years. The most clinical manifestation from diagnosis of vasculo-BD were oral ulcers nine, followed by skin involvement eight, genital ulcers five, arthritis five, ocular involvement four, gastrointestinal two. Six patients, vascular involvement occurred at the same time as diagnosis of vasculo-BD. Three patients had arterial lesions, six patients had venous lesions. All patients received corticosteroids, two patients were treated with pulsed methylprednisolone. Five patients were treated with Colchicine. Eight patients recurred during an observation period, two patients were treated with pulsed methylprednisolone, five patients with pulsed cyclophosphamide, four patients with Infliximab. They have relatively good prognosis. It is important that early identification and management of diagnosis, because vasculo-BD lead to lethal complication as aneurism and pulmonary embolism.

## P2-217

### Frosted branch angiitis associated with Behçet's disease at diagnosis: A case report

Naoko Konda, Tsuyoshi Kobashigawa, Yuko Okamoto, Masanori Hanaoka, Daisuke Hoshi, Hisae Ichida, Yasuhiro Katsumata, Yasushi Kawaguchi, Hisashi Yamanaka  
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

[Case] A 29-year-old male with recurrent oral aphthous ulcers and acneiform eruption was admitted to previous hospital complained with visual loss and high grade fever. Before 5 days, diagnosing influenza B with headache and fever, he took laninamivir. After, erythema nodosum (EN) and ophthalmalgia were occurred. Visual loss, uveitis and retinal bleeding were indicated before 3 days. Fulfilled Behçet's disease (BD) criteria, PSL 20 mg/day was started, and steroid injected in Tenon capsule, so his fever and EN were improved, but his iritis and angiitis lasted. On the 10th day, transferred ours with inflammation: CRP 13.6 mg/dL, and frosted branch angiitis (FBA) was recognized. Steroid pulses following PSL 40 mg/day and cyclosporine was performed, as serum and vitreous humor infection and malignancy screening were negative. His ocular lesions were improved. [Clinical Significance] FBA was rare in uveitis, typical pathology was sheathing of retinal vessels as frosted branch of a tree, and it may correlate of immune-complexes and deposit in retinal vessels. FBA caused auto-immune/inflammatory disease in which BD was the most reported: 7 cases found in PubMed and some Japanese reports found in JAMAS. Steroid pulse was almost effective for FBA was recommended, similarly in our case.

## P2-218

### An autopsy case of Behçet's disease with vascular involvement complicated with repeated pulmonary thromboembolism

Daisuke Tsukui<sup>1</sup>, Hirotohi Kikuchi<sup>1</sup>, Mai Okubo<sup>1</sup>, Kurumi Asako<sup>1</sup>, Maki Takayama<sup>1</sup>, Akiko Okamoto<sup>1</sup>, Toshihiro Nanki<sup>2</sup>, Tamiko Yanagida<sup>1</sup>, Hajime Kono<sup>1</sup>, Shunsei Hirohata<sup>3</sup>

<sup>1</sup>Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan, <sup>2</sup>Teikyo Academic Research Center, Teikyo University School of Medicine, Tokyo, Japan, <sup>3</sup>Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan

Conflict of interest: None

Purpose: Vascular involvement (VBD) is a serious manifestation of Behçet's disease. It is controversial whether anti-coagulant therapy is

necessary in VBD. We report an autopsied patient who died of VBD complicated with repeated pulmonary thromboembolism (PTE). Case report: A 37-year-old man had an initial attack of PTE due to deep vein thrombosis (DVT). A filter was inserted into the inferior vena cava (IVC) and warfarin was started. After that, he was diagnosed as VBD because of recurrent oral aphthous ulcer, folliculitis and genital ulcer. He was complicated with ulcerative colitis and was treated with lymphocyte apheresis (LCAP) therapy. During LCAP, he developed PTE attack. Despite anti-coagulant therapy, he died. Autopsy findings showed massive thrombus formation in IVC 10 cm distal from the filter and the bilateral pulmonary arteries. Histological study showed that many thrombi were fresh and consisted of red blood cells and fibrin. Some thrombi were being organized with recanalization. There were no findings of obvious vasculitis in the pulmonary artery and IVC. Conclusions: Our patient died of exacerbation of DVT and PTE occurred despite anti-thrombotic therapy. These observation underscore extensive anti-thrombotic therapy with strict monitoring is required for VBD.

## P2-219

### A Case of Behçet's Disease Complicated with Common Iliac Aneurysm

Yuta Baba, Ryo Takahashi, Hidekazu Furuya, Sho Ishii, Takeo Isozaki, Sakiko Isojima, Yusuke Miwa, Tsuyoshi Kasama  
Division of Rheumatology, Department of Medicine, Showa University School of Medicine

Conflict of interest: None

A 45-year-old man, he was diagnosed with Behçet's disease (BD) from oral aphtha, arthralgia, erythema nodosum (EN), thrombophlebitis, and epididymitis four years ago. Two years ago, the patient came to our hospital because of the recurrence of EN on his lower extremities. Because of multiple deep venous thrombosis (DVT), we could diagnosis vasculo-BD. The symptoms were improved by steroid therapy and azathioprine. One year ago, the recurrence of EN and DVT lower extremities. We resumed the treatment with prednisolone 30mg/day and warfarin. Six months ago, the symptoms worsened, accordingly the steroid dose was increased. Although EN was improved, the patient was admitted to our hospital because of highly sustained observation of lower grade fever and inflammation, abdominal pain, persistent malaise of his right lower extremity, and common iliac aneurysm inspected by CT scan. We diagnosed with an aneurysm associated with vasculo-BD from the clinical course, and performed steroid pulse therapy, cyclophosphamide therapy, and stent grafting. As a result, the symptoms were improved. [CLINICAL SIGNIFICANCE] The reports of BD complicated with aneurysm are occasionally seen, but we report the case based on the clinical observation because it is a relatively rare case.

## P2-220

### The pulmonary arterial aneurysms in vascular Behçet's disease: Clinical and radiologic remission after infliximab therapy

Tadahiro Tokunaga<sup>1</sup>, Shotaro Yamamoto<sup>2</sup>, Koji Endo<sup>3</sup>, Takuya Tanimoto<sup>1</sup>, Hiroyuki Maeda<sup>1</sup>

<sup>1</sup>Department of Respiratory Medicine and Rheumatology, Hiroshima Prefectural Hospital, Hiroshima, Japan, <sup>2</sup>Department of Internal Medicine, Jinsekikogen Town Hospital, Hiroshima, Japan, <sup>3</sup>Department of General Medicine, Hiroshima Prefectural Hospital, Hiroshima, Japan

Conflict of interest: None

A twenty-five year old woman visited a general hospital complaining cough, hemoptysis, chest pain, and exertional dyspnea. By that time, she had been suspected to have Behçet's disease (BD) because of thrombophlebitis and multiple stomatitis. Blood test showed the inflammation and the computed tomography revealed the left pulmonary arterial aneurysm. She was referred to our hospital and diagnosed as having vascular BD by the presence of recurrent oral aphthous ulcers, thrombophlebitis, folliculitis-like rashes and the vascular lesion, based on the diagnostic criteria (Ministry of Health, Labor and Welfare, 2003). Although the case was considered as an indication of the strong immunosuppressive therapy, the patients refused the use of corticosteroids and cyclophosphamide, concerning about the side effects including cosmetic aspects and the repro-

ductive dysfunction. In these regards, infliximab therapy (5mg/kg) was initiated. After the first administration of infliximab, the respiratory and mucocutaneous symptoms resolved completely. The diameter of the left pulmonary arterial aneurysm reduced (22 to 15 mm) at 14 weeks after the initiation of the therapy. The importance of the novel therapy for this very rare case, especially when in a young woman, will be discussed.

### P2-221

#### **Infliximab for chronic progressive neuro-Behçet's disease: An 8-year follow-up study**

Kurumi Asako<sup>1</sup>, Mai Okubo<sup>1</sup>, Daisuke Tsukui<sup>1</sup>, Akiko Okamoto<sup>1</sup>, Hirotohi Kikuchi<sup>1</sup>, Toshihiro Nanki<sup>2</sup>, Hajime Kono<sup>1</sup>, Shunsei Hirohata<sup>3</sup>  
<sup>1</sup>Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan, <sup>2</sup>Teikyo Academic Research Center, Teikyo University School of Medicine, Japan, <sup>3</sup>Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan

Conflict of interest: None

[Objectives] Although chronic progressive neuro-Behçet's disease (CPNB) is a rare and intractable condition, it is previously reported that infliximab (IFX) is effective for treating CPNB at least within half a year. Here we report the long-term follow up of CPNB patients who received IFX. [Methods] Medical records of 7 CPNB patients who received IFX were retrospectively reviewed. [Results] Three patients remained on IFX therapy without clinical progression of CPNB. One patient stopped receiving IFX after 6 months because of the good clinical course, and showed no sign of recurrence so far with weekly low dose MTX only. Progression of neurological manifestations was observed in 3 patients. 2 of those worsened still continued IFX therapy with brainstem atrophy in MRI and CSF IL-6 levels between 50-200 pg/mL, and one discontinued IFX because of withdraw consent after 1 years. These 3 patients once tried discontinuation of IFX, but all of them resumed within 6 months because of marked increase of CSF IL-6 levels. [Conclusion] These results imply that IFX has been well tolerated and showed a beneficial effect for the treatment of CPNB. Future studies are required for patients in whom intractable CPNB does not respond to MTX and IFX.

### P2-222

#### **A case of infliximab-responsive pubic osteitis as a main presentation of undifferentiated spondyloarthritis**

Toshiaki Shimizu, Hiroyuki Yamashita, Yuko Takahashi, Hiroshi Kaneko, Akio Mimori  
Division of Rheumatic Diseases, National Center for Global Health and Medicine

Conflict of interest: None

[Objectives] A case of infliximab-responsive pubic osteitis as a main presentation of undifferentiated spondyloarthritis [Methods] A 28-year-old man with a history of lumbar and hip pain for some years was referred to us with a one-month history of severe groin pain. He had consulted a local doctor, but plain radiography and lumbar magnetic resonance imaging had shown no abnormalities, and tramadol-acetaminophen combinations had been ineffective. Physical examination revealed no abnormalities. Blood tests showed a white blood cell count of 11510/ $\mu$ L and C-reactive protein level of 2.8 mg/dL. MRI showed T1-low and fat-suppressed T2-high regions spreading from both sides of the pubic symphysis. Fludeoxyglucose positron emission tomography showed abnormal uptake. Pubic osteitis or osteomyelitis was suspected. Bed rest had no effect and his pain worsened, suggesting it was not caused by mechanical irritation. Blood cultures were negative. A pubic bone biopsy showed no infection. We diagnosed pubic osteitis due to undifferentiated spondyloarthritis. [Results] First administration of infliximab completely treated the pain, and the CRP level reduced. [Conclusion] To our knowledge, this is the first report of infliximab-responsive pubic osteitis as a main presentation of spondyloarthritis.

### P2-223

#### **One case of Ankylosing Spondylitis, which became a secondary invalid case of Infliximab by neutralizing antibody expression; A case report**

Takashi Imuro<sup>1</sup>, Keishi Marumo<sup>2</sup>, Tetsuro Nishizawa<sup>2</sup>  
<sup>1</sup>Department of Orthopaedic Surgery, Atsugi City Hospital, Kanagawa, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Jikei University, Tokyo, Japan

Conflict of interest: None

[Case] 54y.o., Male. The patient was admitted to our department complaining of the sternum joint pain and back pain. Bamboo spine deformity, the sacroiliac joint deformity belonging to Gade4 on right side and Grade3 on left side of modified New York criteria were observed in plain X-ray image. Subjective symptoms were improved by the start of treatment with INF 5mg/kg, BASDAI score was significantly improved in 5.0 to 3.4 and CRP value was also normalized. Subjective symptoms relapsed at 46 weeks, transient poison measles-like rash appeared at 62 weeks. To further similar symptomatic infusion reaction appeared at 70 weeks, the administration of INF was discontinued and anti-TNF antibody was detected in a blood test. For this reason, we changed to the bi-weekly administration of adalimumab (ADA) 40mg. BASDAI score was improved from 5.7 to 3.7, CRP value became negative again. [Discussion] Since INF is a chimeric monoclonal antibody, neutralizing antibodies often expressed, especially without the combination of MTX. Therefore, when administration of INF for AS, it is necessary to pay an adequate attention to the changes of the clinical symptoms. During the detection of anti-INF antibody, for shortening or increased dosing interval INF is not permitted, it is useful to change the drug to ADA.

### P2-224

#### **A case of psoriatic arthritis progressing to spine ankylosis despite TNF $\alpha$ inhibitor therapy**

Daigo Taniguchi<sup>1</sup>, Daisaku Tokunaga<sup>1</sup>, Ryo Oda<sup>1</sup>, Shinji Akioka<sup>2</sup>, Yutaka Kawahito<sup>3</sup>, Toshikazu Kubo<sup>1</sup>  
<sup>1</sup>Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>2</sup>Department of Pediatrics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>3</sup>Department of Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>4</sup>Department of Dermatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: None

[Clinical significance] We describe a case in which TNF $\alpha$  inhibitor therapy remarkably improved clinical symptoms, but ankylosis developed. As no recommendations exist for cases progressing into ankylosis, we wish to highlight this problem. [Case] A 49-year-old man with psoriasis vulgaris from age 20 years was previously treated with ultraviolet therapy and etretinate. He consulted our department aged 38 years for hip and buttock pain and polyarthritis. At the first visit, he had multiple arthritis and swelling in the large joints, and CRP, rheumatoid factor and antinuclear antibody were all negative. There was no obvious joint destruction or spine ankylosis on X-ray. NSAID and MTX therapy did not halt symptom progression so infliximab was commenced when the patient was 41 years old. Although joint and skin symptoms improved initially, ossification developed in the hip and spine. Intensifying infliximab therapy did not prevent the progress of ossification in the hip and spinal ankylosis. [Discussion] NSAIDs and TNF $\alpha$  inhibitors can suppress spinal ossification in some but not all cases of ankylosing spondylitis. Therefore, we must determine how to prevent progression into spinal ankylosis.

### P2-225

#### **Digititis and tarsitis were important diagnostic clues in a patient with undifferentiated spondyloarthritis**

Takuji Nakamura, Masao Tanaka, Haruka Iwao, Hironori Shimizu, Tomomi Sato, Akio Nakajima, Miyuki Miki, Tomoyuki Sakai, Yoshimasa Fujita, Yasufumi Masaki, Toshihiro Fukushima

Conflict of interest: None

[Introduction] Spondyloarthritis (SpA) is the disease characterized by inflammatory back pain (IBP) and asymmetrical or lower limb-dominant distal joint inflammation. This is a case of undifferentiated SpA in which digititis and tarsitis were important clues to the diagnosis. [A case report] A 44-year-old woman had suffered from low back pain since the age of twenty. In January 2014, she consulted with an orthopedic surgeon in our hospital because of one-year lasting pain and decreasing movement range in bilateral foot joints. MRI detected bone edema in a left cuboid bone. In February, she had her right 2-5<sup>th</sup> finger MP/PIP/DIP joint swelling, pain and progressive contracture. In April, she was introduced to us. Schober's test was positive (2cm). MRI didn't show sacroiliac joint inflammation but right finger synovitis. She was diagnosed with undifferentiated SpA, because her symptom set of IBP, synovitis and alternative buttock pain satisfied a classification criterion for SpA (ESSG) while it didn't satisfy that for classical SpA such as ankylosing spondylitis (AS). Rehabilitation and adalimumab with oral MTX gave her some relief from the symptoms. [Discussion] We should remember SpA in examining a patient with asymmetrical distal joint inflammation.

## P2-226

### Examination of the joint ultrasonographic observation at the time of the polymyalgia rheumatic (PMR) diagnosis according to their outcomes

Yoshie Gon, Kenta Misaki, Rintaro Saito, Yuri Nakamura, Takumi Nagamoto, Hisayo Horiuchi, Hirotaka Yamada, Toshihiko Yokota  
Kurashiki Central Hospital, Okayama, Japan

Conflict of interest: None

[Objectives] PMR is a disease which needs diagnosis by exclusion. After diagnosis some refract to glucocorticoid (GC) treatment, and some prove to be seronegative rheumatoid arthritis (RA). We classified PMR patients according to their outcomes and examined their features with Musculoskeletal Ultrasound (MSKUS) at diagnosis. [Methods] We retrospectively analyzed age, CRP, WBC, MMP-3, Alb, Hb, and scales of MSKUS before a medical treatment start at our hospital from 2009 to 2014. MSKUS was performed at both shoulders with subdeltoid bursa, biceps tendon and glen humeral cavity. The degree of Grey scale (GS) and power Doppler (PD) activity were scored on a four-point semi-quantitative scale. Each patient's total GS and PD scores of shoulder joints were calculated by summing the corresponding scores. [Results] Among 46 patients, 10 were classified as GC response group, 6 as poor response, and 11 were diagnosed as RA. In comparison of poor response group (D group) and RA group, GS of D group was significantly higher than RA group at the time of diagnosis (D group: mean GS 4.2±0.4 vs. RA group mean GS 6.7±0.8  $p=0.044$ ). [Conclusion] At the time of PMR diagnosis, the high grade of GC of shoulder joint ultrasound suggest a possibility of RA.

## P2-227

### Three cases of paraneoplastic syndrome mimicking polymyalgia rheumatica

Maki Takayama, Hirotohi Kikuchi, Kurumi Asako, Hajime Kono  
Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Introduction] We experienced 3 cases of paraneoplastic syndrome mimicking polymyalgia rheumatica (PMR) in patients who were transferred to our hospital because of polyarthritis and fever. **Case 1:** A 57-year-old man with bilateral wrist pain, neck pain, and fever was admitted to our hospital. There were no obvious abnormal imaging findings. However, sputum cytology was class V. In bronchoscopy, an obstructive lesion was observed in the left lower lobe inlet region. The patient was diagnosed with small cell lung cancer. **Case 2:** A 75-year-old woman had neck and bilateral shoulder, hip, and thigh pain with fever. She was

diagnosed with PMR and treated with PSL. During screening for malignancy, she required urgent surgery for intussusception caused by cecal cancer. **Case 3:** A 68-year-old woman with bilateral knee pain, left elbow pain, shoulder pain, weight loss, and fever visited our hospital. After an examination, she was diagnosed with PMR and treated with PSL at 10 mg/day. 3 years later, she had bilateral wrist and neck pain while taking PSL at 3 mg/day. Dizziness developed and we again performed a whole body examination. Ovarian cancer was detected. [Discussion] Screening for malignancy should be performed at onset of PMR and in cases with flare-up of PMR-like manifestations.

## P2-228

### A case of RS3PE syndrome with reversible digital contracture

Yuta Yamaguchi<sup>1</sup>, Akihiko Nakabayashi<sup>1</sup>, Sara Murakami<sup>1</sup>, Madoka Morimoto<sup>1</sup>, Johji Kohno<sup>2,3</sup>, Kazushi Konma<sup>1,2</sup>, Yoshinori Katada<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Sakai City Hospital, Sakai, Japan, <sup>2</sup>Sakai City Hospital, Sakai, Japan, <sup>3</sup>Department of Orthopedics, Sakai City Hospital, Sakai, Japan

Conflict of interest: None

(Case) A 70-year old woman with 3-month history of polyarthralgia and hands and feet edema was admitted to our hospital. She had severe digital contracture in both hands. Laboratory tests showed C reactive protein of 12.5 mg/dl. Neither rheumatoid factor nor ANA was detected. Hand X-rays only showed an increase in soft tissue density. Tenosynovitis of digital flexor tendons was revealed by a fat suppression T2-weighted magnetic resonance imaging, suggesting this caused the digital contracture. With the diagnosis of remitting seronegative symmetric synovitis with pitting edema (RS3PE), 15mg of prednisone was started, resulting in good response not only in arthritis and edema but also in the digital contracture.

## P2-229

### Safety and efficacy of mizoribine for polymyalgia rheumatica: Case series of 47 cases

Ryo Rokutanda, Mitsumasa Kishimoto, Hiroyuki Baba, Shunya Kaneshita, Masei Suda, Chisun Min, Yuri Ohara, Hisanori Shimizu, Tokutaro Tsuda, Kenichi Yamaguchi, Akira Takeda, Yukio Matsui, Masato Okada  
Immuno-Rheumatology Center, St. Luke's International Hospital, Tokyo, Japan

Conflict of interest: None

[Objectives] To report the safety and efficacy of mizoribine (MZR) for polymyalgia rheumatic (PMR). [Methods] We extracted all the patients who were given MZR for treatment of PMR during the period of July 2009 to June 2014. Retrospective medical charts review were performed to check the patients' background, duration and drug survival rate of MZR use, and reasons for discontinuation. Serum inflammatory markers and dose of corticosteroids at the time of last follow-up were compared those at the time of MZR initiation. [Results] Forty-seven PMR patients (16 male and 31 female, mean aged 73.5±7.9 year old) were treated by MZR during the study period. Mean disease duration at the time of MZR initiation and mean duration of MZR use are 415±61 days and 423±345 days, respectively. Twelve patients had discontinued MZR, and the reasons of discontinuation are as follows: remission (4 patients), ineffectiveness (4 patients), and adverse reaction (4 patients). The dose of PSL at the time of last follow-up was significantly lower than the PSL dose at the time of MZR initiation. [Conclusion] MZR is effective and well-tolerated in patients with PMR.

## P2-230

### The clinical consideration of 16 polymyalgia rheumatica of our institution containing 6 examples of glucocorticoid medical treatment resistance

Tomofumi Marumo, Yuko Fujii, Minoru Muraki  
Aobakai Hitotsubashi Hospital, Tokyo, Japan

Conflict of interest: None

[Objectives] Treatment with glucocorticoid (GC) is the preferred therapy for polymyalgia rheumatica (PMR), but some patients show poor responses. Alternative therapies for patients with GC resistance have not yet been established. [Methods] In our institution we examined the clinical background of 16 cases PMR (January 2008 to October 2014) which met the diagnostic criteria of Bird. [Results] The average is 77.8 years-old. Treatment were started 2.0 month. Temporal arteritis concurrence 1 case, RA factor positivity 3 cases and 3 antinuclear antibody positivity. GC treatment start is an average of 17.8mg. Complete remission group (CR) is 6 cases. GC treatment resistance group (RG) is 6 cases. GC given dose at the time of a treatment start is 16.7 mg of CR and a treatment period are 23.2 month. RG need 19.2 mg and treatment restrengthening the GC given dose after 20.7 month. GC given dose after restrengthening is 3~10 mg. 2 cases use MTX. All the progress is 40 month. RG has more amounts of GC starts than a CR, the necessity for treatment strengthening is at an early stage, and the therapeutic process had become a long period of time. [Conclusion] The case of treatment resistance is also in PMR over a long period of time. We thought that cures other than GC treatment needed to be developed.

### **P2-231**

#### **A clinical study of five cases of relapsing polychondritis**

Takuma Koga, Naomi Yoshida, Shinjiro Kaieda, Morihiko Tajiri, Yukiko Kunitake, Daisuke Wakasugi, Masaki Okamoto, Masaki Tominaga, Hiroaki Ida

Division of Respiriology, Neurology and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Fukuoka, Japan

Conflict of interest: None

Relapsing polychondritis (RP) is a rare multisystemic disease characterized by the flaring-remitting of the cartilaginous structures including external ears, nose, joints, larynx, and tracheobronchial tree. Etiology is still unclear, however, an immunological disorder is involved. We analyzed clinical features of five patients with RP. They consisted of 3 males and 2 females, with ages of onset ranging from 53 to 72. Diagnosis was made for 1 month to 6 months after the hospital visit. At the onset of disease, the auricle redness was observed in 2 patients. Chronic cough was initial symptom in other 2 cases. Puffy finger was found in one patient. Only one patient received medical treatment for bronchial asthma. The medium duration for developing airway disease was 7 years. One patient was dead suddenly by acute respiratory failure. Antibodies to type II collagen were positive in 4 patients. Corticosteroids were given to all patients and immunosuppressive agents such as cyclosporine A were added after the airway involvement was worsened. In our observation, two of five patients were died of respiratory failure. Airway involvement associated with RP takes the fatal outcome, thus, an early diagnosis is important.

### **P2-232**

#### **A case of relapsing polychondritis (RP) complicated with sarcoidosis and hemophagocytic syndrome (HPS)**

Daisuke Fujishiro, Atsushi Kobayashi, Kensaku Okamoto, Kouhei Eguchi, Keiji Komura, Satoru Kodama, Katsutoshi Mizumoto, Ryota Yoshimoto, Yuichi Makino, Masakazu Haneda

Division of Metabolism and Biosystemic Science, Department of Medicine, Asahikawa Medical University, Asahikawa, Japan

Conflict of interest: None

A 60-year-old man was admitted to our hospital with complaints of fever and systemic pain in November 2011. He developed chondritis of ears and nose, and bilateral scleritis. The diagnosis of relapsing polychondritis (RP) was established by the biopsy of the left auricular cartilage. Treatment with prednisolone (PSL) 30 mg/day was initiated and his symptom was disappeared. In June 2012, azathioprine was added because of relapse, but he was admitted again in July because of persistent fever. Progression of leukopenia and anemia was observed, and the diagnosis of hemophagocytic syndrome (HPS) was made by bone marrow aspiration (BMA). He was treated with 1 g/day methyl-PSL (mPSL) for 3 days followed by PSL 50 mg/day. Leukopenia and anemia were temporarily im-

proved, but recurred as PSL was tapered. Second BMA revealed hemophagocytosis and epithelioid cell granuloma. We diagnosed as HPS complicated with sarcoidosis, and 6 mg/week methotrexate (MTX) was added to PSL 30 mg/day. He was recovered from pancytopenia and dosage of MTX was increased to 10 mg/week, and PSL was tapered to 20 mg/day. There are some reports about RP with other autoimmune disease, however, only 3 cases are reported for coexisting RP and sarcoidosis as far as we searched. We will present this case with references.

### **P2-233**

#### **Three cases of patients with proteinase-3 antineutrophil cytoplasmic antibody-positive inflammatory bowel disease**

Kazuhiro Ito, Toshio Odani, Michihito Kono, Shinji Fukaya, Hideaki Kikuchi

Hokkaido P.W.F.A.C Obihiro-Kosei General Hospital

Conflict of interest: None

Inflammatory bowel disease (IBD) is the generic name for ulcerative colitis (UC) and Crohn disease. This differentiation cannot always be definitively made, and these cases are characterized as cases of indeterminate colitis (IC). We experienced three IBD patients with positive proteinase-3 antineutrophil cytoplasmic antibody (PR3-ANCA). Case 1: A 61-year-old man was admitted because of hematochezia and diarrhea. The serum level of PR3-ANCA was 20.3 U/ml. He was diagnosed with ulcerative proctitis by endoscopic findings (EF). He was treated with mesalazine, apparently leading to remission. Case 2: A 75-year-old-man admitted because of diarrhea and abdominal pain. The levels of PR3-ANCA was 23 U/ml. A diagnosis of IC was made by EF. Only with bowel rest, the volume of diarrhea decreased. Case 3: A 49-year-old woman was admitted because of diarrhea, and hematochezia. She was diagnosed with left-sided colitis by EF. The levels of PR3-ANCA was 41.8 U/ml. With combination therapy of mesalazine and azathioprine, her stool condition improved. In all cases, titer of PR3-ANCA decreased by treatment. PR3-ANCA is used for diagnosis and activity index of granulomatosis with polyangiitis. PR3-ANCA may be useful for evaluation of the disease activity index in IBD.

### **P2-234**

#### **Medical care for the patients with rheumatoid arthritis (RA) and human T-cell leukemia virus type 1 (HTLV-1) infection**

Shunichi Miyauchi, Kunihiko Umekita, Akihiko Okayama

Department of Rheumatology, Infectious Diseases and Laboratory Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan

Conflict of interest: None

[Objectives] To know whether HTLV-1 infection has any impact on the medical care of RA patients in Japan. [Methods] Survey by the questionnaire to Japan College of Rheumatology authorized 560 institutions. [Results] Two-hundred fifty one institutions (45%) responded. HTLV-1 antibody test was performed in 30% of institutions (60% of institutions in Kyushu area); however, the frequency of the test was less than once a month in most of them. The doctors, who reported to have experienced adult T-cell leukemia (ATL) or HTLV-1-associated myelopathy (HAM), was about 5%, suggesting the occurrence of certain number of HTLV-1 related diseases in RA patients. Many doctors (70-80%) answered that they are not certain whether they should test HTLV-1 before they treat RA using biologics or immunosuppressants. The frequency for the requests from doctors for more information about HTLV-1 and medical care for RA patients was high (80%). [Conclusion] The HTLV-1 test is considered to be performed in not small number of RA institutes. Certain number of ATL or HAM occurs in RA patients in Japan. These data suggest that more information should be provided to the RA specialists. Moreover, further study about HTLV-1 and RA is necessary.

### **P2-235**

#### **A case of catastrophic *pseudomonas* pneumonia that was complicated by CNS lupus treated with cyclophosphamide pulse therapy**

Hiroto Nakano, Atsuhisa Ueda, Naomi Tsuchida, Yumiko Sugiyama, Yosuke Kunishita, Reikou Kamiyama, Kaoru Minegishi, Maasa Hama,

Ryusuke Yoshimi, Yohei Kirino, Mitsuhiro Takeno, Yoshiaki Ishigatsubo  
Department of Internal Medicine and Clinical Immunology, Yokohama  
City University Graduate School of Medicine, Yokohama, Japan

Conflict of interest: None

[Case] A 43 year-old female was diagnosed with SLE 9 years ago for having malar rash, oral ulcer, cytopenia, ANA and anti-DNA antibody. Two months before this admission, she was diagnosed with NPSLE for having ds-DNA Ab elevation and aseptic meningitis. She was treated with corticosteroid and cyclophosphamide pulse therapy (IVCY). Three weeks after the 2nd IVCY, she visited the ER because of right shoulder pain, shaking chills and fever. Chest X-ray revealed consolidation in right upper lung field, which was suspected to be pneumonia or alveolar hemorrhage. Although piperacillin tazobactam was started at the time of admission, oxygenation, hypotension and X-ray findings rapidly aggravated. The patient was moved to the ICU and mechanical ventilation was started. Blood and sputum culture revealed *pseudomonas* pneumonia and septicemia. The patient was extubated on 15th day of admission, and was discharged on 46th day without major complications. [Discussion] Several risk factors for infectious events in SLE were met; high anti-DNA antibody level, low complement level, high dose corticosteroid, high dose IVCY. Even without neutropenia, severe *pseudomonas* infections may occur in patients who receive IVCY.

## P2-236

### Analysis of Prognostic Factors and Change of Infections Complicated in Patients with Rheumatoid Arthritis in the last 15 years

Yoichiro Akiyama, Takeo Sato, Takamasu Murosaki, Katsuya Nagatani, Seiji Minota  
Division of Rheumatology and Clinical Immunology, Department of  
Medicine, Jichi Medical University, Tochigi, Japan

Conflict of interest: None

[Objective] To clarify the prognostic factors and the change of infections in patients with rheumatoid arthritis (RA) during the evolution of antirheumatic therapy in the last 15 years. [Methods] We retrospectively reviewed data of hospitalized patients with RA complicated with infections from 1999 to 2013, which were divided into 5 quintiles. We investigated the prognostic factors, clinical characteristics of RA, and the change of infections. [Results] By multivariate analysis of all patients, the mortality was associated with *Pneumocystis jirovecii* pneumonia (PCP) (Odds ratio 13.43,  $p < 0.001$ ), age (Odds ratio 1.51,  $p = 0.006$ ), and steroid-use (Odds ratio 1.35,  $p = 0.006$ ). PCP was associated with MTX- (Odds ratio 1.70,  $p < 0.001$ ) and steroid-use (Odds ratio 1.50,  $p < 0.01$ ). There was no association between biologic DMARD (bDMARD)-use and PCP or mortality. From 1st to 5th quintile, MTX-dose and the bDMARD-use increased. The respiratory system was most frequently infected in each period. The mortality in each period did not increase. The frequency of PCP increased through 1st and 5th quintile. [Conclusion] The type of infections complicated with RA has changed, but the mortality didn't increase. Attention and prevention will be necessary to avoid development of PCP when using MTX or steroid.

## P2-237

### A case of rheumatoid arthritis complicated with acute glomerulonephritis during etanercept therapy

Takahiro Seno<sup>1,2</sup>, Takashi Kida<sup>2</sup>, Daigo Taniguchi<sup>3</sup>, Aiko Tominaga<sup>2</sup>, Risa Sagawa<sup>2</sup>, Amane Nakabayashi<sup>2</sup>, Ken Murakami<sup>2</sup>, Aihiro Yamamoto<sup>2</sup>, Masataka Kohno<sup>2</sup>, Toshikazu Kubo<sup>1,3</sup>, Yutaka Kawahito<sup>2</sup>

<sup>1</sup>Department of Rheumatic Diseases and Joint Function, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>2</sup>Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>3</sup>Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: Yes

[Case] 74-year-old male. He was pointed out interstitial pneumonitis on chest X-ray and positive finding in rheumatoid factor by medical

checkup, and he was diagnosed as rheumatoid arthritis in 2009. After the diagnosis, he was treated with sulfasalazine (SASP) and bucillamine (BUC) were followed by administration with tacrolimus (TAC). In 2012, we started etanercept (ETN) at 25mg/week, but it wasn't enough effective. Within a half year, we escalated dose of ETN at 50mg/week and added on prednisolone (PSL) at 5mg/day. His disease control was well afterwards, but protein urea and occult blood in urine were detected from about May, 2014. In June, urine protein was worsening at 6.16g/gCr and urine RBC 10-19/HPF. We stopped ETN. Renal biopsy showed IgA dominant necrotizing crescentic glomerulonephritis. Despite cessation of ETN, renal function was not improved. In consideration of strong immunosuppression, we made diagnosis as post infectious acute glomerulonephritis. Therefore we stopped all the DMARDs and started PSL at 35mg/day. After PSL treatment, protein urea was improving to 1.84g/gCr, but serum creatinine was worsening about 2mg/dl. We report a case of rheumatoid arthritis complicated with treatment-resistant acute glomerulonephritis.

## P2-238

### One case of the rheumatoid arthritis that produced purulent gonitis and leg abscess during biological drug use

Hiroshi Yonezu, Hiroshi Mikami  
Department of Orthopaedic Surgery, Oe Kyudo Hospital, Tokushima, Japan

Conflict of interest: None

[Introduction] We experienced the RA case of purulent gonitis and leg abscess introduced to our hospital for deep vein thrombosis (DVT) doubt. [Case] 65 years old woman. She received TCZ from 2013. The swelling of the left leg developed from the middle of January, 2014. After consulting the nearby doctor, she was introduced for DVT doubt to our hospital because D-dimer was a high price. There was not the fever and was 7.3 µg/dl of D-dimer, CRP 0.49 mg/dl, WBC 2960/µL, neutrophils 65.4%. After performing contrast-enhanced CT, left purulent gonitis and leg abscess was doubted. Staphylococcus aureus was detected by the stab culture of the knee joint and leg abscess department. [Results] We enforced knee joint synovectomy, resection of abscess and drainage. The decrease in liquid retention in the knee joint, and the disappearance of the abscess were accepted in the CT of 3 weeks after operation. She left the hospital 4 weeks after the operation. [Conclusion] An ascent of fever and CRP is not seen even if patient produce infection in the TCZ dosage case, and attention is necessary because a diagnosis of the infection may be late. When the swelling of lower limbs was accepted in a case receiving biological drug, it was thought that we should take infection into consideration.

## P2-239

### A case of iliopsoas muscle abscess with rheumatoid arthritis on low dose glucocorticoid and csDMARD

Kyoichi Nakajima  
Department of Rheumatology, National Hospital Organization Higashi-Saitama Hospital, Saitama, Japan

Conflict of interest: None

[Background] Rheumatoid arthritis (RA) patients rarely complicated iliopsoas muscle abscess (IPA) before, but not in biological era. I report a case of IPA with RA on low dose glucocorticoid (GC) and conventional synthetic DMARD (csDMARD). [Case] A 77-year-old woman with a 30-year history of RA on bucillamine 100 mg daily and prednisolone (PSL) 5 mg daily. She presented with gait disturbance 4 month ago, following right hip pain. She admitted to the hospital because C-reactive protein (CRP) was elevated. Antibiotics was given, but her temperature spiked to 39 degree C. Increasing dose of PSL to 20 mg daily made her afebrile and reduced CRP. She relapsed her pain after tapering PSL to 15 mg daily. On admission to my hospital, blood culture grew *Escherichia coli*, and abdominal CT and MRI revealed right IPA and vertebral osteomyelitis at the level of L1. Antibiotics reduced her pain and IPA in size 34 days after admission. As recovery was very slow, she moved to the orthopedic hospital. Posterior spinal fusion from Th12 to L4 and anterior curettage of the bone of L2/3 were performed and she could discontinue

antibiotic therapy. [Clinical significance] We should remind a combination of low dose GC and csDMARD can be a cause of rare intractable infection.

## P2-240

**Pulmonary manifestation of patients with rheumatoid arthritis (RA)**  
Hiroki Hayashi<sup>1</sup>, Kazuo Yoneda<sup>2</sup>, Mami Inayama<sup>2</sup>, Asami Fukuya<sup>2</sup>, Akane Abe<sup>2</sup>, Takashi Haku<sup>2</sup>

<sup>1</sup>Center for Clinical Education, Tokushima Prefectural Central Hospital, Tokushima, Japan, <sup>2</sup>Department of Respiratory Medicine and Thoracic Oncology, Tokushima Prefectural Central Hospital, Tokushima, Japan

Conflict of interest: None

[Objectives] To investigate the incidences and clinical features of pulmonary involvement in patients with RA. [Methods] This was a retrospective review of 117 RA patients who were examined at Tokushima Prefectural Central Hospital in the period from January 2009 to October 2014. [Results] Anti-CCP antibodies were detected in 38 (32.4%) of the 117 RA patients. 55 RA patients were treated with methotrexate (MTX) or Biologic agents. In 117 cases, the most common pulmonary involvement was interstitial pneumonia (IP, 49 cases, 41.9%). There were 37 cases of infection (32.5%), 8 cases of lung cancer (6.8%), 5 cases of pleuritis, 4 cases of bronchiectasis, 4 cases of post-inflammatory change, 3 cases of emphysema, 1 case of rheumatoid nodule, 1 case of sarcoidosis, 1 case of metastatic tumor, 1 case of multiple nodular shadows, 1 case of kyphosis and 1 case of bronchial asthma. 7 cases died from respiratory failure. [Conclusion] Our study revealed that various pulmonary involvement are observed in RA patients. It is important to consider the possibility of acute exacerbations of IP including drug induced pneumonitis or opportunistic infections in RA patients who have received MTX or Biologic agents.

## P2-241

**Organizing pneumonia (OP) and Bacterial pneumonia (BP) in Rheumatoid arthritis (RA)**

Satoru Teshigawara<sup>1</sup>, Takashi Shimizu<sup>1</sup>, Takuro Nii<sup>1</sup>, Akiko Yura<sup>1</sup>, Maiko Yoshimura<sup>1</sup>, Eriko Tanaka<sup>1</sup>, Soichiro Tsuji<sup>1</sup>, Yoshinori Harada<sup>1</sup>, Masato Matsushita<sup>1</sup>, Shiro Ohshima<sup>1,2</sup>, Yukihiko Saeki<sup>1,2</sup>

<sup>1</sup>NHO Osaka-minami Medical Center Dept. of Rheumatology and Allergology, Kawachinagano, Japan, <sup>2</sup>NHO Osaka-minami Medical Center Dept. of Clinical Research, Kawachinagano, Japan

Conflict of interest: None

[Background] In RA, pulmonary complications are often seen. Both OP and BP can occur during the course of RA. However, we often have difficulties with differentiating OP from BP, because both present similar infiltrative shadows in chest computed tomography (CT). Corticosteroid is the standard therapy for OP, on the other hand, antibiotics is necessary for BP. Procalcitonin (PCT) is diagnostic marker of septicemia. [Objectives] To evaluate the usefulness of PCT for differentiating OP and BP [Methods] Twelve RA patients diagnosed as pneumonia with infiltrative shadows in chest CT were enrolled. Four patients were successfully treated only with prednisolone (PSL), diagnosed as OP. Another four patients, diagnosed as BP, were successfully treated with only antibiotics (ABx). The rest of four patients were treated with Abx, followed by PSL therapy referred to as MIX. All patients received blood exams before treatment and C-reactive protein (CRP), WBC and PCT were measured. Comparisons of levels within each group were analyzed using the Mann-Whitney's U-test. [Results] PCT levels in OP were significantly lower than those in BP ( $p=0.0304$ ). In CRP and WBC, there were no differences between OP and BP. [Conclusion] PCT is a useful marker for differentiating OP from BP in RA patients.

## P2-242

**An autopsy case of acute exacerbation of rheumatoid arthritis-associated interstitial pneumonia with serum IL-6 remarkable elevation**

Yuko Kashihara, Masao Tamura, Makoto Terada  
Itami City Hospital

Conflict of interest: None

[Case] A 69-year-old woman who had a 2-year history of active interstitial pneumonia (IP) with RA. Combination therapy of PSL and tacrolimus (TAC) was able to control her rheumatoid lung. In 2014, nausea and loss of appetite appeared, she suspended treatment with PSL and TAC for five days. As fever (38 °C) and cough appeared, she was admitted to our hospital. Serum KL-6 level was elevated, and chest CT showed increased interstitial shadow in the diffuse lung. *Haemophilum influenza* was detected with her BAL fluid. So we diagnosed acute exacerbation of IP with bacterial infection and started to treat antibiotics and m-PSL pulse therapy. Then bacteria completely became extinct in sputums, but IP followed a course of aggravation. Although cyclophosphamide pulse and cyclosporin A were combined to steroid therapy, respiratory failure and CT image did not improve. And serum IL-6 level increased to 664pg/ml, thus we were administered tocilizumab (8mg/kg). But she was died of progressive respiratory failure. The histological findings of the lung showed diffuse alveolar damage (DAD), nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP) and bronchitis.

## P2-243

**Current status of hepatitis B infection in our hospital outpatient**

Makoto Kondou, Hiroshi Kataoka, Masaya Mukai  
Rheumatology and Immunological Internal Medicine, Sapporo City General Hospital

Conflict of interest: None

[Objectives] This time, B hepatitis prevention guidelines for immunosuppressed patients has been changed. Screening has become more stringent. In our hospital the majority of patients had been measured only HBs-Ag. We did the screening test along the guidelines in all patients being administered immunosuppressive. [Methods] Through April to June 2014, we measured HBs-Ab, HBe-Ab and HBV-DNA if necessary, in 471 cases. In Cases which had results of HBV antibody positive and HBV-DNA negative, we measured HBV-DNA in 1-3 months intervals. [Results] In 471 cases, 7 cases became the HBV-DNA positive. For cases that HBV-DNA positive became clear, we asked our hospital liver specialist to follow up. Only one case became the adaptation of nucleic acid analog treatment. Remainders are under observation without intervention. In such cases, HBV-DNA changed negative from positive repeatedly. [Conclusion] Not all patients of HBV-DNA positive would be necessary for nucleic acid analog treatment.

## P2-244

**Clinical Features of Rheumatoid Arthritis Patients who hospitalized with interstitial pneumonia**

Jun Fujimoto, Jun Fukui, Hachiro Konaka, Takahiro Kawasaki, Takayoshi Morita, Yasuhiro Kato, Yoshiyuki Mori, Kumiko Kobayashi, Hiroshi Fujiwara  
Division of Rheumatology, Osaka General Medical Center, Osaka, Japan

Conflict of interest: None

[Objectives] To clarify clinical features of RA patients who hospitalized due to interstitial pneumonia (IP). [Methods] We retrospectively examined the medical records of hospitalized RA patients with IP from April 2008 through August 2014. [Results] We found 45 events consist of 41 patients. Chest CT findings on admission were mainly UIP pattern (UIP) (19cases, 42%) and NSIP pattern (NSIP) (11cases, 24%). We compared the characteristics of these two groups. Pre-existing IP was found in 12 in UIP group and 2 in NSIP group ( $P=0.017$ ). Anti-CCP antibodies levels were 279.9±207.8 in UIP group and 159.0±203.8 in NSIP group (0.207). The number of cases received steroid pulse therapy 9 (47.3%) and 3 (27.2%) ( $P=0.279$ ), while immunosuppressive drugs were used in 8 (42.1%) and 2 (18.2%) ( $P=0.181$ ), respectively. Among all the patients, 7 cases whose CT consisted of 3 UIP, 3 DAD, and one NSIP pattern received mechanical ventilation. Four patients died and three of them died of lung lesion. Among those, 2 patients had DAD pattern on admission, while one had UIP. [Conclusion] In our study, 8.9% of the RA patients hospitalized due to IP died. UIP group received numerically more frequently steroid pulse therapy and immunosuppressive agents, although it

is not statically significant.

## P2-245

### Differentiation of lung dominant type of interstitial pneumonia with systemic sclerosis and dermatomyositis

Yumiko Wada, Takuya Kotani, Takeshi Shoda, Takayasu Suzuka, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa  
Rheumatology, Department of Internal Medicine I, Osaka Medical College

Conflict of interest: None

[Objectives] We investigated useful clinical and radiological findings to differentiate lung dominant type of interstitial pneumonia with systemic sclerosis (SSc-LDIP) and dermatomyositis (DM-LDIP). [Methods] Nine SSc-LDIP and 12 DM-LDIP patients were included. [Results] SSc-LDIP patients were more elderly. DM-LDIP was more likely show arthritis and higher KL-6. There was no significant difference on chest HRCT findings between SSc-LDIP and DM-LDIP. [Conclusion] Careful observation of physical, laboratory and radiological findings are needed to differentiate between SSc-LDIP and DM-LDIP.

## P2-246

### Acute respiratory distress syndrome involvement in Adult-onset Still's disease: A case report

Yoko Miura, Mika Kobuna, Rika Okada, Masanobu Horikoshi, Shoko Kobayashi, Shigeko Inokuma  
Japanese Red Cross Society, Tokyo, Japan

Conflict of interest: None

[Introduction] Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder characterized by fever, rash, arthritis, sore throat, hepatosplenomegaly, lymphadenopathy, leukocytosis, liver enzyme elevation, and high serum level of ferritin. Although few cases may have pulmonary involvement, acute respiratory distress syndrome (ARDS) involvement in AOSD is rare. [Case report] A 47-year-old female was diagnosed with AOSD in 2001 based on symptoms and signs including fever, rash, arthritis, liver enzyme level elevation, leukocytosis, and high serum level of ferritin. At first, corticosteroid worked well. But during the tapering, fever and arthritis recurred. MTX, TAC, IFX were added. One year before, cortisol-producing tumor in her left adrenal gland was removed. At April 2014, oxygenation got worse and ferritin level was increased. Consolidation was seen severely whole lung field on CT. High dose corticosteroid therapy under supported respiration cured her from ARDS. [Discussion] Only few cases of ARDS in AOSD are reported to date. Therapy of ARDS is established yet. In our AOSD case, corticosteroid therapy cured ARDS.

## P2-247

### Dyspnea on a patient with Rheumatoid Arthritis and Sjogren Syndrome

Hidefumi Fukuda<sup>1</sup>, Atsushi Hashimoto<sup>1</sup>, Hideki Ogihara<sup>1</sup>, Kanako Iwata<sup>1</sup>, Koichiro Horie<sup>1</sup>, Hirotsuka Tsuno<sup>1</sup>, Misato Kawakami<sup>1</sup>, Toshihiro Matsui<sup>1</sup>, Akiko Komiyama<sup>3</sup>, Shigeto Tohma<sup>2</sup>

<sup>1</sup>Department of Rheumatology, Sagami National Hospital, National Hospital Organization, <sup>2</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, National Hospital Organization, <sup>3</sup>Department of Clinical Laboratory, Sagami National Hospital, National Hospital Organization

Conflict of interest: None

A 40 year-old woman treated with salazosulfapyridine and tacrolimus for rheumatoid arthritis (RA) and Sjögren Syndrome complained dyspnea. She had neither hypoxia nor significant findings on chest X-ray, CT and echocardiogram. Arterial blood gas analysis (ABG) showed pH: 7.37 and HCO<sub>3</sub><sup>-</sup>: 14.9 mmol/L. She was diagnosed as distal renal tubular acidosis (RTA) and started sodium bicarbonate. Subsequently she admitted our hospital with hypoxia. The pH and HCO<sub>3</sub><sup>-</sup> on ABG was normal but CT revealed ground-glass opacity of the lung. She was diagnosed as My-

coplasma pneumonia with the elevated antibody. But her symptom still continued after treatment with antibiotics. Respiratory function test showed obstructive pattern (FEV1%: 53%) and lung ventilation scintigraphy showed lack of air ventilation at both lower lungs. We diagnosed obliterating bronchiolitis (BO), which could presents air trapping on expiratory phase HRCT but our patient did not. Even if a patient suffers from dyspnea, RTA does not show hypoxia and BO can presents normal finding on CT. These involvements are often difficult to be diagnosed but should be cared about.

## P2-248

### An autopsy case of ankylosing spondylitis complicated with severe cardiac dysfunction

Masami Tokura, Marina Tsuchida, Hiroyuki Hagiya  
Department of Rheumatology, Yokohama City Minato Red Cross Hospital, Yokohama, Japan

Conflict of interest: None

A 41-year-old Japanese man suffered from right knee arthritis at the age of 28. He was diagnosed with ankylosing spondylitis (AS) based on bilateral sacroiliitis and limited motion in the lumbar spine at the age of 33. Despite treatment with anti-inflammatory and anti-rheumatic drugs, arthritis remained active and high serum C-reactive protein level persisted. We could not use biologics, because he refused our recommendation. At the age of 36, he underwent cardiac catheterization because cardiac dysfunction was suspected by echocardiogram. But coronary arteries were intact and left ventricular wall motion was within normal limit. Because his disease had progressed, he had difficulties of walking and received visiting care. At the age of 40, he was transferred to our hospital due to popliteal artery occlusion. In addition, he was diagnosed with congestive heart failure (CHF) based on pulmonary congestion and a severely impaired left ventricular ejection fraction (LVEF) of 14%. Despite treatment for CHF, LVEF remained low. About 8 months after starting therapy of CHF, he died due to bacterial pneumonia. Autopsy findings show normal cardiac valves and ventricular wall. There are no pathological findings accounting for severe cardiac dysfunction.

## P2-249

### Successful treatment for pulmonary hypertension with immunosuppressive therapy in a patient with mixed connective tissue disease

Go Murayama<sup>1</sup>, Yuri Yamazaki<sup>2</sup>, Shinya Kawano<sup>1</sup>, Yutaka Nakiri<sup>2</sup>, Masakazu Matsushita<sup>1</sup>, Ken Yamaji<sup>1</sup>, Naoto Tamura<sup>1</sup>, Yoshinari Takasaki<sup>1</sup>  
<sup>1</sup>Department of Internal Medicine and Rheumatology Juntendo University School of Medicine, <sup>2</sup>Department of Internal Medicine and Rheumatology Juntendo University School of Medicine, Nerima, Tokyo, Japan, <sup>3</sup>Division of Cardiology, Department of Internal Medicine Juntendo University School of Medicine, Nerima, Tokyo, Japan

Conflict of interest: None

This report described a 25 years-old female mixed connective tissue disease (MCTD) patient presenting pulmonary hypertension, successfully treated with immunosuppressive therapy. She was admitted to our hospital, and she was diagnosed as having MCTD because of Raynaud's phenomenon, dyspnea on exertion, arthritides, and elevated level of anti-U1 RNP antibodies. A diagnosis of pulmonary hypertension was made by echocardiography and catheterization study. Pulmonary artery pressure and pulmonary artery resistance declined and returned gradually to normal during a period of three months with prednisolone and azathioprine therapy. Although pulmonary hypertension is one of fetal complications with MCTD, a successful therapy for the pulmonary hypertension with MCTD has not been established yet. We considered that immunosuppressive therapy might be useful to control the pulmonary hypertension with MCTD and could improve the prognosis of MCTD.

## P2-250

### Clinical characteristics and comparing of 16 cases of rheumatoid arthritis (RA) complicated with iatrogenic immunodeficiency-associated lymphoproliferative disorders (LPD)

Takeo Kudo, Toshihiro Tono, Hiroaki Taguchi, Yasuo Osone, Yutaka

Okano  
Center of Rheumatism, Collagen Disease and Gout, Kawasaki Municipal  
Hospital, Kawasaki, Japan

Conflict of interest: None

Recent strengthen medication against RA might increase the number of patients with iatrogenic immunodeficiency-associated LPD (IIDA-LPD; by WHO classification). We experienced three cases since it was reported in this Society in 2013, and compared the clinical features and other reports. Their mean age was 64.1 y/o; male/female ratio was 4:12; and their mean disease duration of RA was 14.9 years. Average dose of methotrexate (MTX) was 8.1 mg/w and 5 patients received TNF inhibitors. Pathological findings revealed many types of LDP with diffuse large B cell lymphoma, Hodgkin's lymphoma, T cell lymphoma, B cell lymphoma in 10, 3, 2, and 1 cases, respectively. Epstein-Barr virus (EBV) dyeing of tumor cells revealed positive in 12 cases. Four cases died, 5 cases recovered by stop administering MTX and TNF inhibitors, and 7 cases achieved remission or improved with chemotherapy against LPD. The results are similar when compared with previous reports. IIDA-LPD is has been suggested that the prognosis has and clinical characteristics is varied.

## P2-251

### Two case reports; Rheumatoid arthritis patients found MTX-related lymphoproliferative disorder when proximal femoral fracture was cased

Mochihito Suzuki<sup>1</sup>, Atsushi Kaneko<sup>2</sup>

<sup>1</sup>Shizuoka Saiseikai General Hospital, <sup>2</sup>Nagoya Medical Center

Conflict of interest: None

[clinical significance] Methotrexate (MTX) is used for many patients now as key drug in rheumatoid arthritis (RA). Various complications by MTX are reported. I experience two cases of RA found MTX-LPD when proximal femoral fracture (PFF) was cased for the perioperative period. [case] Case 1, 71 female, disease period 24 years. She takes MTX8mg/week for two years, thereafter uses Abatacept for two months. She performs operation of PFF. Abnormal shadow is recognized with chest X-ray and shows it with sIL-2R 512 U/ml and diagnose it with a malignant lymphoma by transbronchial lung biopsy. Because I follow it up only by MTX cancellation, and a tumor reduces. Case 2, 79 female, disease period 18 years. She takes MTX6mg/week for ten years. She performs operations of PFF. There is an inflammatory reaction and pleural effusions on the postoperative 7th day. Her condition deteriorates on the 14th day, and sIL-2R 20,900 U/ml and MTX-LPD is diagnosed. On the 15th day she dies of MTX-LPD. [consideration] It is reported that the association between MTX and LPD in the RA. It is important to always take possibility of the MTX-LPD onset into consideration that MTX-LPD is accepted with PFF like this time and may be behind with a diagnosis again for the perioperative period when it uses MTX.

## P2-252

### Immunodeficiency-associated lymphoproliferative disorders caused by cyclosporine A in a patient of mixed connective tissue disease

Takuya Matsumoto<sup>1</sup>, Hitoshi Yamasaki<sup>1</sup>, Jun Ishizaki<sup>1</sup>, Sachiko Onishi<sup>1</sup>, Koichiro Suemori<sup>1</sup>, Eiji Sada<sup>2</sup>, Masaki Yasukawa<sup>1</sup>, Hitoshi Hasegawa<sup>1</sup>

<sup>1</sup>Department of Hematology, Clinical Immunology and Infectious Diseases, Ehime University Graduate School of Medicine, <sup>2</sup>Department of Medical Technology, Ehime Prefectural University of Health Sciences

Conflict of interest: None

63-year-old female was admitted to our hospital because of high fever, polyarticular pain, low complement titer, high anti-RNP antibody titer and Raynaud's phenomenon, and she was diagnosed as mixed connective tissue disease (MCTD). The treatment of prednisolone (PSL) (15mg per day) was undergone for one year but her symptoms have worse. She treated by a steroid pulse therapy and 100mg of cyclosporine A (CsA) was immediately added to steroid therapy to control the disease. With successful Immunno-suppressive therapy, MCTD had been controlled well for seven years. In 2014, however, she had persistent fever for one

month and left pharyngeal ulceration with high uptake of FDG PET-CT. She was performed oral biopsy, and was suspected NK/T cell lymphoma. After CsA was stopped, her general condition was getting better and her pharyngeal ulceration also improved. In this case, immunodeficiency-associated lymphoproliferative disorders (ID-LPD) appear to be caused by immune-suppressive condition with CsA. Since there are only a few cases of ID-LPD caused by CsA, we report it with a review of the literature.

## P2-253

### A case of systemic lupus erythematosus with pancytopenia and lymphadenopathy, which was needed to differentiate malignant lymphoma

Yoshihito Hayami, Nobuyuki Takahashi

Nagoya City Wset Medical Center

Conflict of interest: None

The patient was 64-year-old woman. She was treated with oral prednisolone 4mg because of systemic lupus erythematosus (SLE). From 2013 February, her urine protein increased, and the renal biopsy was revealed to lupus nephritis V type. She was treated with prednisolone up to 20mg and added tacrolimus 1.5 to 2mg. Then the prednisolone was tapered. From 2014 April, because her fever increased gradually, she was hospitalized on July 9 because of the increased frequency of her fever. The whole body CT revealed the swellings of the cervical, subclavian, abdominal aortic and iliac lymph nodes, and malignant lymphoma was suspected on this CT images. Although tacrolimus has been discontinued after admission, the pancytopenia progressed and DIC also suspected. Gabexate Mesilate and Dalteparin sodium infusions were administrated. Cervical lymph node biopsy specimen showed necrotizing lymphadenopathy, but not malignant lymphoma. After tacrolimus discontinuation, both lymph nodes enlargement and pancytopenia were improved.

## P2-254

### Clinical effectiveness of Igaratimod in rheumatoid arthritis

Etsuko Maeshima<sup>1,2</sup>, Kanako Furukawa<sup>3</sup>, Shinichiro Maeshima<sup>4</sup>, Yasutaka Yamauchi<sup>5</sup>

<sup>1</sup>Department of Health and Sport Management, Osaka University of Health and Sport Sciences, <sup>2</sup>Third Department of Internal Medicine, Wakayama Medical University, <sup>3</sup>Department of Internal Medicine, Kainan Iryou Center, <sup>4</sup>Second Department of Rehabilitation, Fujita Health University Nanakuri Sanatorium, <sup>5</sup>Department of Rheumatology, Naga Hospital

Conflict of interest: None

[Objectives] To examine the clinical effectiveness of Igaratimod in rheumatoid arthritis. [Methods] Five patients with rheumatoid arthritis (RA) treated with Igaratimod and followed up for three months from June to October, 2014 were recruited. Their average age was 59.3±15.4 years old and all of them were women. Three cases were treated with methotrexate (MTX) and the dose was 6-10mg/week. Three cases were treated with prednisolone (PSL) and the dose was 2-7.5mg/day. Etanercept (ETN) was used for 2 cases in dose of 50 mg/week. Two cases were classified Stage II and 3 cases were classified Stage III, and 2 cases were classified Class II and 3 cases were classified III. DAS28-CRP, VAS, CRP, MMP-3, the dose of MTX and PSL, and concomitant drug reduction and/or cancellation were evaluated at 0, 1, and 3 month after the starting of Igaratimod. [Results] No significant changes were shown in DAS28-CRP, CRP, MMP-3, and the dose of MTX and PSL. VAS at three months (51±22mm) significantly decreased in comparison with VAS at just before the administration of Igaratimod (70±19mm) (p<0.05). [Conclusion] The effect of Igaratimod on VAS was recognized three months later of the administration, but it was thought that it would take time more for the improvement of the disease activity.

## P2-255

### Investigation of nutritional assessment in patients with rheumatoid arthritis

Momoko Chikugo<sup>1</sup>, Jun Kishi<sup>2</sup>, Yuko Toyoda<sup>2</sup>, Hiroshi Kawano<sup>2</sup>, Yasuhiko Nishioka<sup>2</sup>



<sup>1</sup>Department of Nutrition and Metabolism, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan, <sup>2</sup>Department of Respiratory Medicine and Rheumatology, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan

Conflict of interest: None

[Objectives] To evaluate body composition, nutritional status in patients with rheumatoid arthritis (RA) and the feasibility of Mini Nutritional Assessment (MNA) to detect rheumatoid cachexia. [Methods] 182 RA patients (143 women) were divided into two groups, good nutrient status and malnutrition, according to MNA. We investigated the detection rate of malnutrition according to MNA with body cell mass (BCM) measured by bioelectrical impedance (BIA) as baseline. Furthermore, we investigate visceral fat area (VFA), because central obesity is common clinical condition in patients with RA. [Results] In the case reduction of BCM is defined as malnutrition, sensitivity of malnutrition by MNA was 64.4% of the women and 50% of the men. In the patients of normal BCM, the rate of VFA  $\geq 100\text{cm}^2$  was high (women  $\geq 60$  years 70.4%, men 85.7%). In low BCM, the rate of VFA  $\geq 100\text{cm}^2$  was more than a half (women  $\geq 60$  years 51.2%, men 55.6%) also. [Conclusion] It was difficult to detect rheumatoid cachexia by MNA. Therefore, body composition measurement should be performed. Furthermore, there were many patients with viscera adipose obesity in RA patients of low BCM, so it was suggested it is important assessment and instruction of not only rheumatoid cachexia but also viscera adipose obesity for the patients.

## P2-256

### Home medical care consultation of Rheumatic diseases at a university hospital

Yumi Yamaguchi<sup>1,2</sup>

<sup>1</sup>Department of Allergy and Rheumatology, The University of Tokyo Hospital, <sup>2</sup>Komeikai Ogikubo Clinic

Conflict of interest: Yes

[Objectives] Older patients with RA often attend to a university hospital until they are impossible to move (i.e. fracture and pneumonia). We researched when older patients with RA become difficult to attend to a hospital and should be introduced to family doctors, while hospital doctors examine the patients with longer intervals. [Methods] Outpatients of our department who needed nursing care, 75-year-old over and have no other family doctor were evaluated their caregivers, medical history, HAQ and CGA. We asked them about their hope for home care medicine or nearby hospital visits and recommended family doctors to take care of their usual conditions, therefore they could attend to a hospital for more detailed examinations once in 3-6 months. [Results] Subjects that make difficult to transit patients to family doctors were (1) long visit hospitals, (2) home alone in everyday situations that family grasp insufficiently. We thought it is necessary to educate patients the importance of family doctors. [Conclusion] Home medical care consultation to outpatients with RA enable the patients to be continued home care in peace. Furthermore it can control emergency hospitalization from unexpected aggravation and leads to the satisfaction of the patients and their families.

## P2-257

### Four cases of hemophagocytic lymphohistiocytosis accompanied with connective tissue diseases

Yuko Toyoda, Terumi Takikura, Mayo Kondo, Seidai Sato, Ryohiko Ozaki, Jun Kishi, Toshifumi Tezuka, Hiroshi Kawano, Hisatsugu Goto, Masaki Hanibuchi, Yasuhiko Nishioka  
Department of Respiratory Medicine and Rheumatology, Tokushima University Hospital, Tokushima, Japan

Conflict of interest: None

We experienced 4 cases of hemophagocytic lymphohistiocytosis (HLH) accompanied with connective tissue diseases. The treatment of the secondary HLH varied a great deal depending on the disease severity. Case 1: A 43-year-old male, who had Raynaud phenomenon since 3 years ago, was admitted to our hospital with fever and headache. He was diag-

nosed mixed connective tissue disease with HLH. He got better by steroid pulse and high-dose steroid therapy. Case 2: A 25-year-old female was admitted to our hospital with fever, butterfly rash, and nephritis. She was diagnosed systemic lupus erythematosus (SLE) with HLH. While steroid pulse therapies were not enough effective, intravenous cyclophosphamide pulse therapy (IVCY) improved her general condition. Case 3: A 22-year-old female was diagnosed SLE because of fever, nephritis and HLH, and was transferred to our hospital. Although the efficacy of steroid pulse therapies was unsatisfactory, IVCY ameliorated her condition. Case 4: A 53-year-old male, diagnosed dermatomyositis (DM) 7 years ago, was admitted to our hospital because of high-grade fever and consciousness disturbance. He was diagnosed HLH accompanied with DM. While steroid pulse therapies and IVIG did not improve his condition, he was successfully treated by intravenous VP-16.

## P2-258

### A study of recent interstitial pneumonia on restrictive hospital in Osaka city For prognosis in caused by idiopathic and collagen diseases

Akihiko Mukai<sup>1</sup>, Megumi Matsueda<sup>1</sup>, Mayumi Kawaguchi<sup>2</sup>, Eiichi Terasawa<sup>3</sup>

<sup>1</sup>Coop Osaka Hospital, <sup>2</sup>Mimihara General Hospital, <sup>3</sup>Nishiyodo Hospital

Conflict of interest: None

[Purpose] pneumonia is a disease, which accounts for many of hospitalization in the regional hospital. Interstitial pneumonia slip into in it. Collagen disease-related lung diseases are also included. This time, we report the study of interstitial pneumonia in our hospital. [Method] We were intended for patients undergoing treatment of interstitial pneumonia on the basis of the discharge summary of the patients admitted to our hospital in the past five years. A classification by the cause and examined its outcome, was also investigated factors affecting prognosis. [Results] 70 cases in all cases. The average age was 79 years. Man: woman was 3:4. Idiopathic 44, collagen disease 20, infectious 5, was a drug-induced one case. From CT images, UIP: NSIP: Others were 4:3:3. Due to collagen disease was RA9, SLE1, SSc4, PM / DM1, MPA4, SS1 example. Death was 21 cases, mortality was 30%. In eight cases in patients with collagen disease, had a high mortality in RA and MPA. High LDH, Pco2>Po2, low Natremia, SP-D/KL-6>0.4 on admission, high LDH maintained group undergoing therapy, honey-comb lung, death discharge there were more often. [Conclusion] Interstitial pneumonia has a high mortality rate. In cases containing many worse prognostic factors, it is necessary to pay more attention.

## P2-259

### Clinical pictures of elderly-onset gout in Japanese patients

Hikota Osawa<sup>1</sup>, Atsuo Taniguchi<sup>1</sup>, Naomi Ichikawa<sup>1</sup>, Yohei Seto<sup>2</sup>, Hisashi Yamanaka<sup>1</sup>

<sup>1</sup>Institute of Rheumatology, Tokyo Women's Medical University, <sup>2</sup>Tokyo Women's Medical University Yachiyo Medical Center

Conflict of interest: None

[Objectives] To investigate the clinical characteristics of elderly-onset gout in Japanese. [Methods] 617 patients who visited our outpatient clinic because of gout attacks in 2007-2009 were included. Patients whose first attacks were at the age > 65 years were defined as elderly-onset group (EG), and those at the age  $\leq 64$  years were defined as non-elderly group (NEG). The clinical findings at their first visits between these groups were compared. [Results] EG consisted of 44 cases (7.1%). Serum levels of uric acid (SUA) in EG (8.6 $\pm$ 1.1 mg/dl) was significantly lower than NEG (9.1 $\pm$ 1.3 mg/dl, p=0.028). The frequency of the previous gouty attacks on the first MTP joint was significantly higher in EG than that in NEG (86.0% vs 60.5%). In the elderly group, as compared with non-elderly group, the proportion of patients with hypertension (58.5% vs 24.5%), chronic kidney disease (42.9% vs 18.0%) and diabetes (11.9% vs 3.2%) was significantly higher. [Conclusion] The elderly group had higher prevalence of co-morbidities, indicating that caution is necessary in therapeutic care in the elderly-onset gout.

## P2-260

### Tuberculosis with suspected rheumatic diseases: 4 cases

Kae Onishi, Naoto Yokogawa, Naonori Tsuda, Takayasu Kise, Yuji Miyoshi, Satoshi Watanuki, Yoshiki Nagai, Eigo Kikuchi, Takahiro Nunokawa, Toshioki Sawaki, Katsuaki Shiroto, Kota Shimada, Shoji Sugii

Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center

Conflict of interest: None

[Introduction] It has been known that tuberculosis (TB) can imitate various other diseases. Here, we report 4 cases of TB that were first suspected of rheumatic diseases. [Cases] Case 1: A 21 year-old man with enthesitis and polyarthritis was first suspected of AS. Later, he developed dry cough and general fatigue. The final diagnosis of reactive arthritis accompanying TB was made from mediastinal lymphadenopathy with positive QFT. Case 2: A 37 year-old man, with surgical history of congenital heart disease, complained of fever lasting 2 months. TB was confirmed by biopsy of bronchopulmonary lymph nodes. Case 3: A 38 year-old woman had sore throat, hepatic dysfunction and cytopenia. Microscopic study of the lung and liver which showed abnormal uptake on PET-CT confirmed the diagnosis of miliary TB. Case 4: A 63 year-old man had mononeuritis multiplex and the cervical lymph node with abnormal uptake on PET-CT. He was diagnosed with TB rather than sarcoidosis, that was confirmed by lymph node biopsy demonstrating epithelioid granuloma and the positive TB DNA-PCR. [Clinical importance] In the practice of rheumatic diseases, we should take into consideration that there is a possibility that TB is hidden in various clinical states.

## P2-261

### Medical care education for connective tissue diseases using a high-performance simulator

Takeo Sakuta, Tomoyuki Mukai, Kyoko Inami, Takafumi Mito, Nami Kosaka, Shunichi Fujita, Yoshitaka Morita

Department of Rheumatology, Kawasaki Medical School, Kurashiki, Japan

Conflict of interest: None

[Objectives] Connective tissue diseases (CTD) cause various systemic organ damage, and we sometimes encounter emergency cases with CTD. A high-performance simulator mannequin is able to imitate various emergency conditions. Using the simulator, learners can experience CTD-related urgent conditions. Here, we report our experiences of the simulator training [Methods] We performed the scenario-based training using the simulator "Simman3G" for the 5<sup>th</sup> grade students. Two or three students per group were trained during the clinical clerkship in our department. We performed 5-minute training and 15-minute debriefing (review session), and afterward a questionnaire survey was conducted. [Results] We surveyed 104 students. Sixty three students participated the simulation-based education for the first time. Most students gave a positive evaluation, such as "The training was very practical." [Conclusion] The simulation-based education was beneficial to students. They realized their insufficient clinical skills, which motivated them to learn medicine more intensively. The current simulators have several problems for applying to the medical care education for CTD, including a limited number of pre-installed CTD-related scenarios and the lack of function for mimicking joint swelling.

## P2-262

### Factors Preventing Patients with Rheumatoid Arthritis from Presenting Their Thoughts to Medical Staff

Yuki Tanaka<sup>1</sup>, Naomi Takahashi<sup>1</sup>, Ako Ohnishi<sup>1</sup>, Makoto Onishi<sup>2</sup>

<sup>1</sup>Department of Nursing, Center for Rheumatic Disease, Dohgo Spa Hospital, <sup>2</sup>Internal Medicine, Center for Rheumatic Disease, Dohgo Spa Hospital

Conflict of interest: None

[Introduction] As some patients passively accept treatment or cannot choose a treatment strategy because of anxiety. [Objectives] To deter-

mine, using a questionnaire, whether patients can sufficiently present their thoughts to medical staff. [Methods] We administered a four-point rating scale-based questionnaire to 69 hospitalized RA patients. [Results] Nine patients responded that they knew little or nothing about RA as a disease, although they had a discharge plan. Four people responded that they did not want to receive any explanation. One patient responded that any explanation would be incomprehensible. Four patients responded that they trusted physician and family decisions. Eight patients believed that sufficient information was exchanged with the physician, while one did not. All patients responded that sufficient information was exchanged with the nurses. Overall, patients wanted medical staff to listen more carefully to them and to communicate more information back to the staff. [Conclusion] Although the information exchange with the medical staff was good, many patients felt that the medical staff failed to sufficiently clarify topics of interest or confusion. We suggest developing an informational, patient-targeted brochure and changing the way information is currently presented.

## P2-263

### Free/low-cost medical business project to rheumatoid arthritis patients

Satoshi Kashiwagi, Yoshikiyo Ohsawa, Hitoshi Nakata, Hiroki Iba  
Amagasaki Medical Coop Hospital

Conflict of interest: None

[Objectives] In some case, it is difficult to consult a doctor and pay medical bill for some rheumatoid arthritis (RA) patients. In our hospital, we practice the free/ low-cost medical business project for those patients. It is a project that patients don't need to pay their medical bill at the hospital. [Methods] We picked up those patients from medical records. We examine their situations of continuations and suspensions. [Results] In 2012, the total number was 211 patients and the RA users were 5. In 2013, the total number was 226 patients and the RA users were 9. In 2014 for 10 month, the total number was 215 patients and the RA users were 8. Some patients stopped to use the project. The reasons were to get the qualification of livelihood protection and get the notebook of a physically handicapped person. [Conclusion] Many RA patients need so much medical bills. The only way for reducing the cost is to get the notebook of a physically handicapped person and use the project high medical care cost. If it is difficult to use those ways, to use the free/low-cost medical business project is a good way. In the future, the patients whose years are over 70 years old need to pay medical bill whose ratio is 20 %. Patients who use the project will increase.

## P2-264

### An attitude survey of patients with rheumatoid arthritis receiving biologics

Michiko Matsuda, Masahiro Saito, Keisuke Nakatsuka  
Japan Community Health Care Organization Fukuoka Yutaka Central Hospital

Conflict of interest: None

[Objectives] We conducted a questionnaire survey of patients with rheumatoid arthritis (RA) receiving biologics (BIO) about their perceptions of BIO in order to clarify the issues related to the treatment. [Methods] For 104 RA patients receiving BIO consulted from June to August 2014, a survey to identify their treatment perceptions (the degree of satisfaction with BIO before and after, problems with BIO, and whether or not to recommend BIO to other RA patients). Furthermore, we conducted an individual interview with 22 RA patients who gave informed consent. [Results] The degree of satisfaction with BIO was 66.4±25.9. The satisfaction score after BIO treatment was increased in 94% of patients. Problems with BIO included expensive treatment in 52 patients, pain of injection in 16, and long restricted time in 16. Whether they would recommend BIO, 23 patients replied 'strongly recommend', 55 replied 'recommend', and 3 replied 'not recommend'. As the reason to recommend, 74 replied that BIO is effective. As the reason not to recommend, 14 replied that BIO is expensive. [Conclusion] The patients receiving BIO were highly satisfied, although there were many problems. It is necessary to hold individual counseling for providing information and utili-

zation of social welfare services.

## P2-265

### Patient preferences and satisfaction in a multispecialty infusion room

Sayuri Sasahara, Noriko Iwata, Masao Sato

Department of Rheumatology, Matsunami General Hospital, Gifu, Japan

Conflict of interest: None

[Objectives] In this study, we assessed patient satisfaction to know whether a separate unit should be recommended when they were administered the infusion drugs in the same room with patients having malignancy. [Methods] A seven-question Likert scale satisfaction survey for patients was developed. (1) I am content having infusions in a cancer infusion center. (2) I am not bothered by the cancer-focused environment. (3) I understand that their disease is not a form of cancer. (4) It will not bother me to enter the Cancer Institute. (5) I have no preference for a non-cancer infusion center. (6) I am not worried about their privacy. (7) It will be no problem for me to move their infusion unit in the future if more space is needed for cancer patients. [Results] Responses were received from 107 patients, 104 rheumatoid arthritis patients, 2 fibromyalgia and 1 spondyloarthritis. Patients had more satisfaction, on all survey items, with the multispecialty infusion room. Analysis demonstrated that patients were satisfied with care in a multispecialty infusion unit and were in favor of continuing their care in this combined room. [Conclusion] Based on these survey conclusions, thus improving quality by including patients in decision-making affecting their care.

## P2-266

### Fact-finding of psychological change and medical treatment actions from the biological preparation introduction of a self-rheumatic injecting it to the present

Etsuko Nishiura, Rie Ino

National Hospital Mechanism Nagoya Medical Center

Conflict of interest: None

[Objectives] Fact-finding of psychological change and medical treatment actions from the biological preparation introduction of a self-rheumatic injecting it to the present [Methods] Inductive methods for conducting qualitative research by semi-structured interview 7 RA patients from each age brackets (20 to 70) having self-injection in our hospital. [Results] Because they wanted to reduce a pain, they did not think that their five of seven people were uneasy. On the other hand, there were two of seven patients who felt prognostic uneasiness of RA before introduction. For them, reduction of a feeling of resistance by the self-injection education and support was seen all the members in seven. Six of seven people talked with a nurse and took measures to get cooperation from a family against it. The change of the everyday life told that six of seven people regained life before becoming, RA. The appropriate care including the removal of the pain may contribute to their everyday stable life. I educate a patient, and it strengthens the relations with the patient that it is understood and reduces their sense of resistance. [Conclusion] Our result would provide an effective enlightenment of the further investigation for the importance of patient education.

## P2-267

### Consideration for the device-change of the self-injection of Etanercept (ETN) from syringe-type (S-type) to pen-type (P-type) as the instructor who guide handling to patients

Kazuyo Miyamoto<sup>1</sup>, Kazuyo Asonuma<sup>1</sup>, Kazunobu Takayanagi<sup>1</sup>, Kenta Misaki<sup>2</sup>, Toshihiko Yokota<sup>2</sup>

<sup>1</sup>Department of Pharmacy, Kurashiki Central Hospital, Okayama, Japan,

<sup>2</sup>Department of Endocrinology and Rheumatology, Kurashiki Central Hospital, Okayama, Japan

Conflict of interest: None

**Purpose:** ETN plays the important role in treatment for RA patients. The P-type came to market in March, 2013 and our hospital introduced it in January, 2014. We carried out a questionnaire targeting patients in

whom the S-type was changed to P-type in order to clarify how to move smoothly from S-type to P-type and continue the self-injection. **Methods:** The questionnaire was passed to all patients the S-type was changed to P-type and guidance of self-injection was given. **Results:** Thirty three of 35 patients returned their questionnaire. Regarding the impression for change from S-type to P-type, good in 33%, no change in 52% and bad in 15% were detected, respectively. The feeling of fear was few in S-type in 46%, same in 45% and few in P-type in 9%. Handling of injection was easier in P-type in 70%, same in 12%, in S-type in 12%. **Conclusions:** The change from S-type to P-type provides improvement of convenience for many RA patients and guidance of handling has become easier. However, there are some issues to improve: the form, size of needle and speed of injection. The improvement of quality of products and method of the guidance of handling is supposed to be necessary to reduce patients who quit the treatment due to difficulty of self-injection.

## P2-268

### A questionnaire surveying of dietary supplement in patients

Natsuki Tomitani<sup>1</sup>, Ai Aritaki<sup>1</sup>, Kihumi Suga<sup>1</sup>, Satoko Nishiura<sup>1</sup>, Yasunori Kobata<sup>2</sup>, Ryota Hara<sup>2</sup>, Takanori Fujimura<sup>2</sup>, Yasuhiro Akai<sup>3</sup>, Takashi Fujimoto<sup>2</sup>, Yasuhiro Tanaka<sup>2</sup>

<sup>1</sup>Nursing Department, Nara Medical University Hospital, <sup>2</sup>Nara Medical University Hospital The Center for Rheumatic Diseases, <sup>3</sup>Nara Medical University Center for Postgraduate Training

Conflict of interest: None

rheumatoidarthritis We report a questionnaire surveying of the use of dietary supplement in rheumatoidarthritis (RA) patients who attended a public program for citizen in Nara prefecture. **Methods:** The public program for RA took place every year since 2010. We designed a questionnaire-based study to examine patient behaviors regarding how they utilize orintake dietary supplement in addition to their ordinary therapy for RA, and their healthconditions and treatment. Participants answered a questionnaire regarding the detailsabout the dietary supplements which they intake or used to utilize. **Results:** A total of participants was 250 to 300 RA patients and their family andavailable survey data were collected from 128 RA patients. The survey data revealed that38 patients (30%) utilize at least one dietary supplement. Only fifteen patients (12%) ofthem, surprisingly, have informed the doctors and nurses in attendance of the use of thedietary supplement. The dietary supplement included vitamins, blueberries, Glucosamine. A few patients, furthermore, intake dietary supplement involving folic acid combined withmethotrexate. **Conclusions:** Doctors and nurses must pay attention to dietary supplements of RApatients and should seek appropriate care consultation. (1258 letters)

## P2-269

### Review of elderly patients with pseudogout-related arthritis in our hospital

Masanori Ono, Midori Oshida

Department of Orthopaedics, Kasai Shoikai Hospital

Conflict of interest: None

[Objectives] Pseudogout-related arthritis is induced by calcium pyrophosphate dihydrate (CPPD) crystals. It frequently develops in elderly persons. In our hospital, in which the Department of Neurosurgery and Department of Cardiology account for 40 and 30% of the total number of hospital beds, respectively, we investigated patients with pseudogout-related arthritis. [Method] The subjects were 17 patients referred to our department with symptoms of arthritis. A diagnosis of pseudogout was made based on intra-articular calcification on plain radiography or CPPD crystals in articular fluid. [Result] The subjects consisted of 5 males and 12 females, with a mean age of 80.7 years. The most frequent site was the knee, followed by the wrist. Most patients showed arthritis symptoms with fever and severe pain. The mean interval from admission until onset was 5.2 days. In all subjects, NSAID administration led to remission within 1 week. However, an improvement was achieved the day after the start of administration in patients in whom intra-articular steroid injection was combined. [Conclusion] In elderly patients with fever or inflammation findings within 1 week after admission, early treatment should be performed, considering pseudogout-related arthritis.

## P2-270

### Results of the linked elbow prosthesis for distal humerus fracture

Takahiro Machida<sup>1</sup>, Keiichiro Nishida<sup>1,2</sup>, Kenzo Hashizume<sup>1</sup>, Ryuichi Nakahara<sup>1</sup>, Ryoza Harada<sup>1</sup>, Masahiro Horita<sup>1</sup>, Toshifumi Ozaki<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, <sup>2</sup>Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

Conflict of interest: None

[Objectives] To investigate results of the linked elbow prosthesis (PROSNAP®) for distal humerus fracture [Methods] We reviewed the records of 8 patients with distal humerus fractures treated by PROSNAP®. They were 3 males and 5 females, with a mean age of 71.1 years. The preoperative conditions of the elbows included 6 fresh fractures {4 multifragmentary fractures and 2 fractures with joint destruction by rheumatoid arthritis (RA)} and 2 non-union fractures. The mean follow-up period was 11.9 months (range, 2-12 months). Clinical evaluations included the range of motion (ROM), Japanese Orthopaedic Association (JOA) elbow score, Mayo Elbow Performance Score (MEPS) and postoperative complications. [Results] The mean of the ROM was 132.5° in flexion, -18.8° in extension, 82.9° in pronation and 85.7° in supination. The postoperative JOA score and MEPS were 90.3 points and 95.7 points, respectively. One patient had postoperative olecranon fracture. There were no other complications. [Conclusion] Several study reported poor results of the open reduction – internal fixation in the case of distal humerus fracture with multifragmentary fracture and joint destruction by RA. The primary joint replacement surgeries using PROSNAP® for these patients resulted in satisfactory results.

## P3-001

### Renal function and the activity of rheumatoid arthritis

Hiroshi Kajiyama<sup>1</sup>, Daisuke Ikuma<sup>1</sup>, Hiroataka Tsuno<sup>4</sup>, Toshihiro Matsui<sup>4</sup>, Atsushi Kaneko<sup>2</sup>, Shinichiro Tsunoda<sup>3</sup>, Koichiro Saisho<sup>3</sup>, Kojiro Sato<sup>1</sup>, Yuji Akiyama<sup>1</sup>, Shigeto Tohma<sup>4</sup>, Toshihide Mimura<sup>1</sup>

<sup>1</sup>Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Iruma, Japan, <sup>2</sup>Department of Orthopaedic Surgery and Rheumatology, Nagoya Medical Center, Nagoya, Japan, <sup>3</sup>Department of Orthopaedic Surgery and Rheumatology, Miyakonojo National Hospital, Miyakonojo, Japan, <sup>4</sup>Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami National Hospital, Sagami, Japan, <sup>5</sup>Division of Rheumatology, Department of Medicine, Hyogo Medical School, Nihinomiya, Japan

Conflict of interest: None

[Objectives] To clarify the correlation between renal dysfunction and disease activity of rheumatoid arthritis (RA). [Methods] Data from 11940 RA patients registered in the large cohort database (NinJa: National Database of Rheumatic Diseases by iR-net in Japan) of 2012 were used. Estimated glomerular filtration rate (eGFR) was calculated, and 7034 patients with eGFR less than 100 were divided into 4 groups, group A: eGFR < 30, group B: 30 ≤ eGFR < 45, group C: 45 ≤ eGFR < 60, and group D: 60 ≤ eGFR < 100. DAS28, CDAI, SDAI, HAQ-DI, ESR, CRP, body weight (BW), age, body mass index (BMI) and treatment were compared among these 4 groups. The correlation of eGFR and DAS28 was analysed. Multiple regression analysis was done. [Results] DAS28, CDAI, SDAI, HAQ-DI, ESR and CRP were highest in group A. eGFR was negatively correlated with DAS28 significantly. Multiple regression analysis showed significant positive correlation of NSAIDs, salazosulfapyridine, methotrexate and bucillamine to eGFR, and significant negative correlation of age, body weight, steroids, ESR and HAQ-DI to eGFR. The significance of DAS was disappeared. [Conclusion] The correlation of RA disease activity to eGFR was confounded by treatment, age, body weight, ESR, and HAQ-DI.

## P3-002

### Analysis of latent renal failure in patients with rheumatoid arthritis

Yoshie Kusunoki<sup>1</sup>, Hirahito Endo<sup>2</sup>, Masayuki Seki<sup>1</sup>, Hiroaki Mori<sup>1</sup>, Yusuke Yamamoto<sup>1</sup>, Aki Shoji<sup>1</sup>, Norihiko Tonozuka<sup>1</sup>

<sup>1</sup>Akisima Hospital, <sup>2</sup>Department of Rheumatology, Jusendo General Hos-

pital

Conflict of interest: None

Chronic renal disease is one of the important comorbidities for treatment in patients with rheumatoid arthritis. To evaluate of latent renal failure in rheumatoid arthritis (RA), we measured the urinary creatinine albumin ratio (ACR) in patients with RA. Methods, we measured ACR 74 patients with RA, Moreover these ACR in patients with RA were compared with that of 32 patients with diabetes mellitus (G1, G2 sage; eGFR over 60ml/min). Results: RA 42 patients mean age 70±13.1 years old, disease duration 8.7 ±6.9 years, female 71.4%. These patients indicated mean eGFR 68.7ml/min and ACR66.4mg/gCr.20 patients (48.7%) adjusted Chronic Kidney Disease (CKD) Criteria by ACR. Although these patients showed normal renal function over eGFR60ml/min CKD 6/21 (22.2%). On the other hands 32 patients with diabetes mellitus (mean age 65.7 years old, female 37.5%) included 6 patients (37.5%) with CKD detected by ACR, which had normal renal function over eGFR60ml/min by Ccr. These data suggested that latent renal dysfunction may be able to detect by ACR in patients with RA. urinary creatinine albumin ratio (ACR). ACR may be useful tool for early detection of renal disorders in patients with RA.

## P3-003

### The association between rheumatoid factor and cardiovascular disease in healthy adults

Chisun Min, Mitsumasa Kishimoto, Shunya Kaneshita, Hiroyuki Baba, Masei Suda, Yuri Ohara, Ryo Rokutanda, Hisanori Shimizu, Tokutaro Tsuda, Kenichi Yamaguchi, Yukio Matsui, Masato Okada  
St.Luke's International Hospital

Conflict of interest: None

[Objectives] To examine whether rheumatoid factor (RF) is associated with cardiovascular disease (CVD) in apparently healthy individuals. [Methods] All participants presenting to the Center for Preventive Medicine at St. Luke's International Hospital from 2004 to 2013 for an annual health screening were included. Using CVD as the primary outcome, we compared several parameters including RF positivity, body-mass index (BMI), abdominal circumference (AC), body fat percentage, systolic blood pressure (SBP), diastolic blood pressure (DBP), lipid profile, HbA1c, fasting blood glucose (FBG), uric acid (UA), C-reactive protein (CRP), percentage of ever-smokers and ever-drinkers, presence of self-reported CVD risk factors including dyslipidemia (DL), diabetes mellitus (DM) and hypertension (HTN), and family history of CVD. [Results] Of 111,021 individuals presenting for health checkup during the study period, 110,856 (99.9%) provided complete datasets regarding our parameters of interests. On univariate analysis, individuals with CVD were more likely to be male, older, and have RF positivity. On multivariate analysis, however, RF positivity was not correlated with CVD after adjustment for clinically established risk factors. [Conclusion] RF does not appear to be correlated with CVD.

## P3-004

### A difference of the remission rate of the rheumatoid arthritis in elderly and non-elderly patients

Hideki Ito, Yuki Fujisawa, Sumie Nakahashi, Kennosuke Mizushina, Sayaka Takenaka, Rie Kujime, Ayako Hirata, Takehisa Ogura, Hideto Kameda

Division of Rheumatology, Toho University Ohashi Medical Center

Conflict of interest: None

[Objectives] Comparison examination of the remission rate of the rheumatoid arthritis (RA) in elderly people and non-elderly patients is carried out. [Methods] Our hospital three months or more by RA patient. The swelling joints 28 (SJC), The oppressive pain joints 28 (TJC), CRP, D-VAS, All of the condition VAS, the sharp pain VAS, and HAQ-DI were evaluated, and it analyzed for 69 examples which could consider each remission of Boolean, SDAI, CDAI, and functional remission. [Results]the number of elderly patients aged 65 and over is 41 among 69 examples (59.4%) elderly people Boolean (29.2% vs. 64.3%) The remission rate

was intentionally low on  $p=0.006$ , SDAI (39.0% vs. 67.9%,  $p=0.027$ ), CDAI (36.6% vs. 67.9%,  $p=0.015$ ), and any remission standard of functional remission (53.7% vs. 82.1%,  $p=0.0204$ ). Examination of the reason looked at the difference clear to the remission rate of the condition VAS in the standard concordance rate of each item of Boolean remission. Furthermore, a synthetic disease activity and HAQ-DI also had SJC, CRP, D-VAS, the sharp pain VAS, and the intentionally same condition VAS at a high price. [Conclusion]elderly RA patient's remission rate was low, and a possibility of being intractable was suggested.

### P3-005

#### Characteristics of late-onset systemic lupus erythematosus experienced in our hospital

Atsushi Nomura<sup>1</sup>, Mitsuru Watanabe<sup>1</sup>, Toshikazu Ozeki<sup>2</sup>, Shun Minatoguchi<sup>2</sup>, Yukari Murai<sup>2</sup>, Rui Kawato<sup>1</sup>, Koji Takasugi<sup>1</sup>, Yukako Oyama<sup>2</sup>, Takuya Hamada<sup>3</sup>, Tatsuhiro Tomino<sup>1</sup>, Hideaki Shimizu<sup>2</sup>, Yoshiro Fujita<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Chubu Rosai Hospital, <sup>2</sup>Department of Nephrology, Chubu Rosai Hospital, <sup>3</sup>Department of Internal Medicine, Chubu Rosai Hospital

Conflict of interest: None

[Objectives] Systemic lupus erythematosus (SLE) that developed 50 years old or older is called "late-onset SLE" and characteristics of patients are different from those of early-onset cases. We investigated the cases experienced in our hospital. [Methods] SLE patients in our outpatient clinic, who receive intractable disease authorization, were investigated by chart review, and characteristics of late-onset and early-onset were compared. [Results] Forty-eight SLE cases were identified and 23 (47.9%) were late-onset. Skin manifestations, butterfly-rash, arthritis were identified in 43.5%, 26.1%, 47.8% of late-onset cases, significantly less than those of early-onset, which were 83.3%, 58.3%, 79.2%. More pleuritis or pericarditis were seen in late-onset, which were 34.8% compared to 8.3% in early-onset. These characteristics were more prominent when patients over 60s and early-onset cases were compared. Anti-Sm antibody was less positive in late-onset, which were 4.8% compared to 25% in early-onset. [Conclusion] In this study, the prevalence of late-onset SLE were higher than previous studies, but characteristics of less skin manifestation, more pleuritis and more pericarditis in late-onset cases were consistent. In this aging society, we have to focus more on late-onset SLE.

### P3-006

#### Diagnosis and treatment of seronegative arthritis patients in a single-center cohort of patients with early inflammatory arthritis

Toshiyuki Aramaki<sup>1</sup>, Kosuke Fukuda<sup>1</sup>, Masataka Umeda<sup>2</sup>, Naoki Iwamoto<sup>2</sup>, Kunihiro Ichinose<sup>2</sup>, Kaoru Terada<sup>1</sup>, Yukitaka Ueki<sup>1</sup>, Atsushi Kawakami<sup>2</sup>

<sup>1</sup>Hakuyujikai Sasebo Chuo Hospital, <sup>2</sup>Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences

Conflict of interest: None

[Objectives] Rheumatoid factor (RF) and anti-CCP antibodies (ACPA) are believed to have association with activity of rheumatoid arthritis (RA). In this study, we investigate what early arthritis patients whose RF and ACPA were both negative at baseline had been diagnosed as and how they had been treated. [Methods] We enrolled early arthritis patients who were referred to our hospital till 2008 to 13 and measured RF and ACPA at the first visit. Diagnosis of RA was used for the 1987 ARA classification criteria or the 2010 ACR / EULAR criteria. [Results] Of 492 patients, 107 (22%) were negative for both RF and ACPA. Excluding other disease, 69 of 102 patients (67.0%) are female. 16 patients fulfilled the 1987 ARA criteria and 16 other patients fulfilled the 2010 ACR/EULAR criteria at the first visit. The average of age and arthritis duration was 62.1 years and 5.5 months respectively. DAS-ESR at start to treat is  $4.8 \pm 1.6$  and CRP was  $1.9 \pm 2.6$ . 49 patients who were initially treated with methotrexate (MTX) have had higher disease activity than 30 patients treated with salazosulfapyridine. [Conclusion] Out of 102, 32 seronegative patients fulfilled either classification criteria of RA at first visit and severe patients were initially treated with MTX.

### P3-007

#### Gender differences in RA

Kiyomitsu Miyachi<sup>1</sup>, Norihiko Koido<sup>2</sup>, Jyunichi Obata<sup>3</sup>

<sup>1</sup>Keigu Clinic, <sup>2</sup>Kawasaki Ryumachi Naika Clinic, <sup>3</sup>Hikari Chuo Clinic

Conflict of interest: None

[Objectives] RA patients were found in 0.5%~1% of the population worldwide. Female RA patients are more prevalent than males with a male to female ratio of approximately 1: 4.8 in Japan and 1: 2.6 in Sweden because of inadequate administration of estrogen in Japan. [Methods] Clinical information regarding the male to female ratio, age of RA onset, interval of years between RA onset and delivery and so on was obtained from 766 RA patients visiting three local outpatient clinics. The OC and HRT use rates were obtained from the website of the National Institute of Health. [Results] The male to female ratio is 5.6 and the peak age of RA onset is 40~59 covering 40% of all RA patients. When incidental RA was adjusted to 1 in nulliparous, the incidental RA rate was 0.5 to 0.7 during 2 to 15 years after delivery. The two percent of OC and HRT use rate in Japan has been much lower than the 20%, 50%, and 60% of those in the USA, Europe and Australia, respectively, for the past 20~30 years. [Conclusion] In general, OC and HRT administration were so infrequent that RA patients were thought to be more abundant in Japan than in Europe.

### P3-008

#### Characteristics and outcomes of rheumatoid arthritis patients who admitted to the emergency center

Nobuyuki Ono, Yukihide Ono, Yukiko Tokuda, Yuri Sadanaga, Satoko Tashiro, Rie Suematsu, Syuichi Koarada, Akihiko Ohta, Yoshifumi Tada  
Department of Rheumatology, Faculty of Medicine, Saga University, Saga, Japan

Conflict of interest: None

[Objectives] We studied the characteristics and outcomes of RA patients who visited the emergency center. [Methods] Retrospectively we collected the data of patients, who visited the emergency center of Saga university hospital between June 2012 and May 2014. [Results] Among 16256 patients who visited there, we found 162 RA patients. Sixty-three admitted to the hospital. The average age of the RA inpatients was 71 years old, and the male to female ratio was 2:5. The main causes of their admission were as follows, 17 infections, 8 cardiovascular diseases, 8 cerebrovascular diseases, 7 bone fractures, 6 gastrointestinal (GI) diseases, 5 respiratory diseases and 12 other reasons. Thirty-five patients needed longer admissions, 14 were operated and 7 were dead. The causes of deaths were 3 respiratory diseases, 1 infection, 1 GI disease, 1 fracture and 1 malignancy. Before admission, the most of the patients were treated with corticosteroids (82.5%), but less with MTX (28.6%) or biologic DMARDs (11%). [Conclusion] RA patients, who admitted through the emergency unit, showed poor outcomes. The patients with high age and corticosteroid usage had the higher risk of emergencies.

### P3-009

#### Clinical Characteristics of Patients with Low Back Pain in a Community Hospital in Japan

Naoho Takizawa, Kenichiro Tokunaga, Masahiro Minoda, Hideto Oshikawa, Kazuo Matsui  
Department of Rheumatology, Kameda Medical Center, Chiba, Japan

Conflict of interest: None

Objectives: Although most cases of low back pain (LBP) are mechanical, there are some exceptions as malignancy, infection and spondyloarthritis (SpA). The aim of this study is to describe the clinical features of patients with LBP. Methods: We retrospectively reviewed the medical records of patients who visited Kameda Medical Center with LBP between April 2013 and July 2014. Data regarding clinical characteristics, red flag signs were collected. Results: There were 581 patients (female 313, mean age 60). Median duration was 14 days. The final diagnosis were Lumbar strain 372 (64%), Osteoporotic compression fracture 83 (14.3%), Herniated disc 43 (7.4%), Spinal stenosis 29 (5%), Degenera-

tive disease 12 (2.1%), DISH 9 (1.5%), SpA 7 (1.2%), Malignancy 2 (0.4%), others 17 (2.9%). 425 (73.1%) patients had red flag sign. Among them, age above 50 was the most common (70.2%), followed by history of malignancy (10.8%), inflammatory back pain (2.2%), steroid use (1.9%). All cases of malignancy (2/2) and 42.9 % (3/7) of SpA had red flag sign other than age. Conclusion: Most cases of LBP were mechanical (98.5%) in our cohort. History and physical examination are valuable for the differentiation of low back pain.

### P3-010

#### How to diagnose elderly-onset rheumatoid arthritis based on the clinical characteristics

Yusuke Yoshida

Emergency Medicine and General Internal Medicine, Rakuwakai Marutamachi Hospital, Kyoto, Japan

Conflict of interest: None

[Objectives] Numbers of patients with elderly-onset rheumatoid arthritis (EORA) are increasing with the aging of society. Their symptoms at onset are more likely to be acute large joint pain or general muscle pain rather than chronic small joint pain. Our aim was to identify how to diagnose EORA. [Methods] We analyzed clinical course and examination findings in 12 EORA patients (5 males and 7 females) who were diagnosed between October 2012 and October 2014. [Results] Median age of disease onset was 82 (69-93) years old. Only 5 EORA patients in our hospital fulfilled 2010 ACR/EULAR Classification criteria for RA; other connective tissue diseases, osteoarthritis, crystal arthritis, infectious arthritis, infective endocarditis and other diseases had to be ruled out. Besides serological and radiographic examinations, we also placed importance on excluding other possible diagnoses by performing culture of blood or joint fluid, and clarifying whether joint fluid contained crystals. For patients in whom a definitive diagnosis was difficult to make, the verification of bone-marrow edema on MRI or synovial thickening on ultrasonography facilitated early diagnosis. [Conclusion] The combination of culture, ultrasonography and MRI may be useful for a definitive diagnosis of EORA.

### P3-011

#### Power Doppler Sonography in Clinical remission status Rheumatoid Arthritis Patients are useful to anticipate future joint destruction

Yukie Saio

Hashima City Hospital

Conflict of interest: None

[Objectives] Musculoskeletal Ultrasonography is useful tool to evaluate status of joints of Rheumatoid Arthritis (RA)-patients. In addition, Power Doppler Sonography (PDUS) is very useful to evaluate inflammatory status of the joints. In this study, we examine the usefulness of Power doppler for DAS28-CRP low clinical remission state patients. [Methods] Total 134 cases of DAS28-CRP low clinical remission state patients were classified into PDUS positive group (n=74) and negative group (n=60) and patient background was compared. [Results] Among several factors (Age, disease duration, MTX dose, duration of remission, TJC, SJC, Pt.VAS, Dr.VAS, CRP, DAS28CRP (4), CDAI, SDAI, MMP-3), duration of remission only showed significant difference between two groups (PDUS positive versus negative group: 1.0+/-1.1 year: 1.6+/-1.4 year; p=0.0028). [Conclusion] It has been reported that joint destruction was observed in DAS28-CRP low clinical remission state patients. Our results indicate that PDUS is useful tool to evaluate whether patients are in structural remission status; i.e. joint destruction free or not and importance of remission period. In addition, PDUS results indicate the inflammatory status of joints well as serum MMP-3 level has influence on PDUS results.

### P3-012

#### Evaluation of radiological progression in autoantibody (ACPA, RF) positive RA after 52 weeks follow-up

Takuya Matsumoto, Toshihisa Kojima, Nobunori Takahashi, Koji Funahashi, Shuji Asai, Toki Takemoto, Kenya Terabe, Yutaka Yoshioka,

Nobuyuki Asai, Tatsuo Watanabe, Yoshikazu Ogawa, Tomonori Kobayakawa, Naoki Ishiguro  
Department of Orthopedic Surgery and Rheumatology, Nagoya University Hospital, Nagoya, Japan

Conflict of interest: None

[Objectives] Some studies have suggested that the status of RF or anti-CCP antibody (ACPA) in RA patients is associated with a clinical response. The aim of this study is to evaluate the influence of autoantibody (ACPA, RF) positivity on radiological progression after 52 weeks follow-up. [Methods] 108 RA patients who started to receive MTX therapy in 6 months from RA onset, were divided into two groups by serum ACPA level at the time of diagnosis; 72 positive group and 36 negative group. And the ACPA positive group was divided again into two group by serum RF level; 58 double positive (DP) group and 14 single positive (SP) group. The disease activities and radiological progression in each group at 52 weeks were evaluated. [Results] There was no significant difference in disease activity on 52 weeks between ACPA positive and negative group. But progression of mTSS in ACPA positive group was greater than that in ACPA negative group (p<0.05). The disease activity and progression of mTSS in DP group and SP group was similar, but joint space narrowing score of DP group was significantly greater than that of single positive group. [Conclusion] In ACPA positive group, especially DP group, radiological joint damage may progress more rapidly than we expect.

### P3-013

#### Serum levels of anti-CCP antibodies in two years follow-up of patients in rheumatoid arthritis treated with biologics

Tetsuya Kaneko<sup>1</sup>, Yasuyuki Tamura<sup>1</sup>, Koichi Okamura<sup>2</sup>, Yukio Yonemoto<sup>2</sup>, Chisa Okura<sup>2</sup>, Takahito Suto<sup>2</sup>, Kenji Takagishi<sup>2</sup>

<sup>1</sup>Inoue Hospital, <sup>2</sup>Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine

Conflict of interest: None

[Objectives] The role of monitoring anti-CCP antibodies of patients with RA treated with biologics has not been elucidated. The aim of this study was to analyze the serum levels of anti-CCP antibodies in the twenty-four month period of follow up with RA patients who were first treated with biologics, to identify peculiarities of therapeutic response. [Methods] Twenty-six RA patients with anti-CCP antibody positive were included in this analysis. Anti-CCP antibodies, CRP, ESR, MMP-3 and DAS28-ESR were determined at baseline (before use of biologics) and after use of biologics (6, 12, 18, 24 months). [Results] In almost patients, the activity of RA was significantly reduced. The level of anti-CCP antibodies decrease during this term follow-up after use of biologics, but that change of anti-CCP antibody was not significantly. Two of twenty-four patients were not decrease of anti-CCP antibodies. However, the clinical response of biological therapy in these patients were sufficient within twenty-four months. [Conclusion] The assessment of anti-CCP antibodies after biological treatment for patients with RA may not provide information of response to biological therapy.

### P3-014

#### There is no relationship between serum 25(OH)D level and disease activity in rheumatoid arthritis patients –the TOMORROW study-

Koji Mandai<sup>1</sup>, Yuko Sugioka<sup>2</sup>, Kenji Mamoto<sup>3</sup>, Tadashi Okano<sup>3</sup>, Masahiro Tada<sup>3</sup>, Shohei Anno<sup>5</sup>, Kentaro Inui<sup>4</sup>, Tatsuya Koike<sup>2,5</sup>, Hiroaki Nakamura<sup>3</sup>  
<sup>1</sup>Shiraniwa Hospital, <sup>2</sup>Center for Senile Degenerative Disorders (CSDD), Osaka City University Medical School, Osaka, Japan, <sup>3</sup>Dept. of Orthopedic Surgery Osaka City University Graduate School of Medicine, <sup>4</sup>Dept. of Orthopedic Surgery Osaka City University Graduate School of Medicine Rheumatism Surgery, <sup>5</sup>Shirahama Hamayu Hospital Welfare Foundation Search Institute for Bone and Arthritis Disease

Conflict of interest: None

[Objectives] The role of serum 25-hydroxycalciferol [25 (OH)D] in the pathogenesis of rheumatoid arthritis (RA) is under investigation. The aim of this study was to evaluate the relationships between 25 (OH)D

level and disease activity in RA patients. [Methods] The TOMORROW is the 10-year cohort study that is comprised of 208 patients with RA and age- and gender-matched 205 controls. 25 (OH)D level and disease activity score (DAS)28-ESR were evaluated at start of the study and after 1 year. Participants were classified in 3 groups by 25 (OH)D levels (low: <15ng/ml, middle, high:  $\geq 20$ ). [Results] 25 (OH)D levels were significantly lower in patients with RA than controls ( $p < 0.001$ ). In RA patients, high 25 (OH)D group tend to have low DAS28, but there was no significant difference in DAS28 among three groups. The age positively correlated with 25 (OH)D ( $r = 0.232$ ,  $p < 0.001$ ), but there was no significant correlation between DAS28 and 25 (OH)D level. After adjusting for age and sex, multiple regression analysis revealed that DAS28 was not associated with 25 (OH)D. The annual change of DAS28 level and 25 (OH)D also did not correlate. [Conclusion] Serum 25 (OH)D levels were significantly lower in patients with RA than controls. There was no association with serum 25 (OH)D level and disease activity in RA.

### P3-015

#### Comparative analysis of the multi-biomarker disease activity (MBDA) score in patients with rheumatoid arthritis treated with Tocilizumab or Adalimumab

Kentaro Hanami<sup>1</sup>, Shintaro Hirata<sup>1</sup>, Nadine Defranoux<sup>2</sup>, Satoshi Kubo<sup>1</sup>, Ipppei Miyagawa<sup>1</sup>, Shunsuke Fukuyo<sup>1</sup>, Norifumi Sawamukai<sup>1</sup>, Kazuhisa Nakano<sup>1</sup>, Shingo Nakayamada<sup>1</sup>, Kazuyoshi Saito<sup>1</sup>, Yoshiya Tanaka<sup>1</sup>

<sup>1</sup>The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, <sup>2</sup>Crescendo Bioscience Inc., South San Francisco, CA, USA

Conflict of interest: None

[Objectives] To compare the multi-biomarker disease activity (MBDA) score and its components in patients with rheumatoid arthritis (RA) treated with Tocilizumab (TCZ) or Adalimumab (ADA). [Methods] Serum concentrations of the twelve biomarkers were measured at 0 and 52 weeks in RA patients (TCZ 50, ADA 49), and combined using the Vectra<sup>®</sup> DA algorithm to obtain MBDA score (1-100). Association of MBDA score with disease activity (DAS28-ESR, CDAI) and joint damage (mTSS) was compared. [Results] Median baseline characteristics [TCZ/ADA] were: age [56.3/56.6 year,  $p = 0.40$ ], disease duration [153.4/95.4 months,  $p = 0.0007$ ], DAS28-ESR [5.5/5.4,  $p = 0.68$ ], mTSS [109.8/62.4,  $p = 0.0006$ ], MBDA score [58.2/61.2,  $p = 0.59$ ]. Over 1 year, DAS28-ESR, CDAI and MBDA score decreased in both groups. Significant difference in percent median change were found in CRP [-99.2/-91.8%,  $p = 0.0006$ ], SAA [-97.0/84.0%,  $p = 0.009$ ], IL-6 [+24/-94.8%,  $p < 0.0001$ ] and MMP1 [-43.4/-24.2%],  $p = 0.027$ . At year-1, ratio of structural remission ( $\Delta$ SHS < 0.5) was higher in TCZ group (90% vs. 75.5%,  $p = 0.049$ ). [Conclusion] MBDA score reflected disease activity and therapeutic response in patients with RA treated with either TCZ or ADA. TCZ may be more likely to inhibit cartilage damage through blocking MMP-1.

### P3-016

#### The time-dependent change of PIP joint circumference with ring gauge before and after commencement

Satoru Nakamura, Ryo Oda, Daisaku Tokunaga, Daigo Taniguchi, Tetsuro Yamasaki, Maki Asada, Hiroyoshi Fujiwara, Toshikazu Kubo  
Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine

Conflict of interest: None

[Objectives] The comparison of PIP joint circumference with ring gauge and ultrasonography, time-dependently before and after commencement. [Methods] Seven RA patients were examined who began receiving MTX or biological agents due to inadequate effectiveness of previous RA treatment. The patients consisted of 6 women and 1 man (mean age: 68.1 years). Evaluation of ultrasonography with Power Doppler and Gray Scale and measurement of PIP joint circumference with ring gauge was performed simultaneously. The maximum diameter of ring gauge of the Japan Custom Size standard was recorded which caused resistance when placed through the IP joint of the thumb or the PIP joint of from index to small fingers. The evaluation was performed before commence-

ment, on the first day after completion of the initial administration, on 2 weeks after, and 4 weeks after. [Results] There was significant correlation between ring gauges and Gray Scale evaluation of MCP joint, the PIP joint, and the wrist joint. A significant correlation was not admitted between ring gauges and Power Doppler. [Conclusion] Ring gauge method is simple, cheap, and easy to repeat. So it is useful method of supplementing the problem of the existing inspection method like the ultrasonography and others.

### P3-017

#### Diagnostic efficacy of joint fluid analysis for primary rheumatoid arthritis

Satoshi Sasaki<sup>1</sup>, Koichiro Takahashi<sup>2</sup>

<sup>1</sup>Sasaki Orthopaedic Clinic, Osaka, Japan, <sup>2</sup>Department of Orthopaedic Surgery, Toneyama National Hospital, Osaka, Japan

Conflict of interest: None

[Objectives] Not all patients with RA conformed to ACR/EULAR criteria 2010 at the first visit. It is difficult to diagnose such as mono- or oligo-arthritis of knee, so we evaluated the diagnostic efficacy of joint fluid analysis from knees of various diseases. [Methods] Joint fluid from patient with knee arthritis were aspirated and analyzed their characteristics (cell numbers, crystal existence) by FALCO. Final diagnosis had been conducted according to each criteria or clinical courses. [Results] From 2004 to 2014, 950 samples from 494 patients were enrolled in this retrospective study. In this period we had not met the patients with infectious arthritis of knees. Patients were separated to four groups (RA: 175 samples, gout: 16, pseudogout: 192, others: 567). Average cell numbers were as follows; 16200 cells per mm<sup>3</sup> (360-162000), 14200 (157-44000), 13600 (90-225000) and 670 (18-22400) for each other. In patients with no crystals, 94% of fluid over 5000 cells per mm<sup>3</sup> were diagnosed RA, while under 1000 cells RA was 2%. [Conclusion] This study showed that joint fluid analysis is useful diagnostic marker for RA. Joint aspiration of mono- or oligo-arthritis of knee may improve the accuracy of RA diagnosis.

### P3-018

#### Neutrophil CD64 for diagnosis of interstitial pneumonia with ground-glass opacity in patients with rheumatoid arthritis

Atsushi Hashimoto<sup>1</sup>, Toshihiro Matsui<sup>1</sup>, Koichiro Horie<sup>1</sup>, Hidefumi Fukuda<sup>1</sup>, Kanako Iwata<sup>3</sup>, Hirotsuka Tsuno<sup>1</sup>, Hideki Ogihara<sup>1</sup>, Misato Kawakami<sup>1</sup>, Akiko Komiya<sup>2</sup>, Shigetoh Tohma<sup>3</sup>

<sup>1</sup>Department of Rheumatology, Sagamihara National Hospital, National Hospital Organization, Kanagawa, Japan, <sup>2</sup>Department of Clinical Laboratory, Sagamihara National Hospital, National Hospital Organization, Kanagawa, Japan, <sup>3</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, National Hospital Organization, Kanagawa, Japan

Conflict of interest: None

[Objectives] Neutrophil CD64 expression (CD64), a diagnostic marker for infection, is also elevated in patients with rheumatoid arthritis (RA) related interstitial pneumonia (RA-IP). We attempt to reveal characteristic laboratory findings including CD64 for the differential diagnosis. [Methods] RA patients who admitted our hospital from 2008 to 2014 with ground-glass opacity (GGO) of the lung and diagnosed as follow were analyzed. Pneumocystis pneumonia (PCP): high serum (1→3)  $\beta$ -D-glucan level and improvement with trimethoprim-sulfamethoxazole. Atypical pneumonia (AT): treated without methotrexate (MTX), negative sputum culture and improved with non- $\beta$ -lactam antibiotics and no corticosteroids. MTX related IP (MTX-IP): negative bacteriological inspections and improved only with withdrawal of MTX. RA-IP: treated without MTX, negative bacteriological inspections and ineffectiveness of antibiotics. [Results] Subjects were 18 PCP, 5 AT, 6 MP and 11 RA-IP. CD64 was high (>3000/cell) in PCP patients and low (<4000) in RA-IP. Elevated peripheral neutrophil counts were found in patients with PCP or RA-IP. KL-6 was not elevated in MTX-IP. RA-IP had lower CD64 than AT. [Conclusion] These characteristics could support diagnosis of those but more samples were needed to avoid wrong diagnosis.

### P3-019

#### Study of hepatitis B markers in patients with rheumatoid arthritis

Yukitomo Urata<sup>1</sup>, Yoshihide Nakamura<sup>2</sup>

<sup>1</sup>Department of Rheumatology, Tsugaru General Hospital, United Municipalities of Tsugaru, <sup>2</sup>Departments of Orthopaedic Surgery, Tsugaru General Hospital, United Municipalities of Tsugaru

Conflict of interest: None

[Objectives] To investigate variations in levels of anti-HBs and anti-HBc, which are recognized as factors affecting reactivation of hepatitis B, in patients with RA and to identify factors associated with decreases in these antibodies. [Methods] For one 139 RA patients with hepatitis B (102 women; mean age, 67.2 years), anti-HBs levels, anti-HBc levels, other hepatitis B markers, and clinical indices were measured at the time of enrollment and 1 year thereafter. Patients whose antibody levels at 1 year after enrollment were lower than those at the time of enrollment were assigned to the decrease group. Multivariate analysis was then performed to identify factors associated with decreased antibody levels. [Results] After 1 year of follow-up, both anti-HBs and anti-HBc levels were significantly decreased ( $445 \pm 430$  mIU/mL,  $p = 0.0001$  and  $6.0 \pm 5.1$  S/CO,  $p < 0.0001$ , respectively). Based on multivariate analysis, the only factor significantly associated with decreased anti-HBc levels was anti-HBc levels at the time of enrollment ( $p = 0.0062$ ; OR, 0.71). The use of steroids was not significantly related to a decrease in anti-HBs levels ( $p = 0.0077$ ; OR, 4.5). [Conclusion] Over the course of RA, both anti-HBs and anti-HBc levels decrease significantly.

### P3-020

#### Comparison of QuantiFERON-TB 2G, 3G and T-SPOT as screening of latent tuberculosis infection in patients with rheumatoid arthritis

Shinya Hirabara<sup>1</sup>, Yuji Hirano<sup>1</sup>, Toshihisa Kojima<sup>2</sup>, Nobunori Takahashi<sup>2</sup>, Masaaki Isono<sup>1</sup>, Naoki Ishiguro<sup>2</sup>

<sup>1</sup>Department of Rheumatology, Toyohashi Municipal Hospital, Aichi, Japan, <sup>2</sup>Department of Orthopedic Surgery, Nagoya University School of Medicine, Nagoya, Japan

Conflict of interest: None

[Objectives] Screening for latent tuberculosis infection (LTBI) is mandatory before initiating methotrexate and biologics in patients with Rheumatoid Arthritis (RA). T-SPOT was introduced in 2012 as a screening of LTBI. For the convenience of blood sampling method, it have been screening using T-SPOT in our hospital from April 2013. The purpose of our study was to investigate the differences of QFT 2G, 3G and T-SPOT in LTBI screening. [Methods] We compared background and judgment results of LTBI screening of 260 cases divided in three groups (QFT 2G, 3G and T-SPOT). [Results] T-SPOT group of disease duration, MTX combination rate and steroid combination rate were significant lower than other groups. Positive rates of QFT 2G, 3G and T-SPOT were 2.8, 10.5 and 5.6%, respectively. ( $p=0.053$ ) The percentages of indeterminate and judgment pending of QFT 2G, 3G and T-SPOT were 9.0, 15.7 and 1.6%, respectively. ( $p=0.002$ ) [Conclusion] In this study positive rate of T-SPOT (5.6%) is lower than that of QFT3G (10.5%), and higher than that of 2G (2.8%). Furthermore because of the low percentages of indeterminate and judgment pending, T-SPOT is excellent as a LTBI screening.

### P3-021

#### Comparisons between ultrasound and arthroscopic findings in the patients with crystal induced arthritis

Hiroaki Hamada<sup>1</sup>, Etsuo Chosa<sup>1</sup>, Koichiro Saisho<sup>2</sup>, Tomohisa Sekimoto<sup>1</sup>

<sup>1</sup>Division of Orthopaedic Surgery, Department of Medicine of Sensory and Motor Organs, Faculty of Medicine, University of Miyazaki, <sup>2</sup>Department of Orthopaedic Surgery, National Hospital Organization, Miyakonojo Hospital

Conflict of interest: None

[Objective] Joint echo and arthroscopic findings in visible gouty arthritis/ CPPD-induced arthritis/ crystal deposition of shoulder cuff were compared. [Methods] Diagnosis of crystalline arthritis assumed the diagnosis at the time of confirming the crystal in arthroscopy. With Hitachi

IIV-VISION 900 and linear probe (14-6MHz) used. Arthroscopy was observed using a Stryker arthroscopic system under lumbar anesthesia. [Results] A double contour sign features a joint echo findings in gout, I admitted the crystal that covers widely the cartilage surface in the arthroscopic findings. Although in CPPD deposition disease is shown to be punctate pattern, in the arthroscopic findings showed the crystals that are patchy deposited in the cartilage. Calcification in the supraspinatus tendon of the shoulder cuff was appeared by adding a tendon incision. Thus the deposition of the crystalline arthritis, I was confirmed that there is a characteristic in each. [Conclusion] Increases further comprehension by comparing the actual direct observation and joint echo findings, it was reaffirmed the usefulness of diagnosis in the echo.

### P3-022

#### Musculoskeletal Ultrasonography of a pinna and joints in a patient with Relapsing Polychondritis

Satoshi Shinohara

Tochigi Rheumatology Clinic, Utsunomiya, Japan

Conflict of interest: None

[Objectives] Usefulness of ultrasound (US) in Relapsing polychondritis (RP) has not been established. I observed a pinna and joints in a patient with RP by US. [Case] A 72-year-old woman was diagnosed as RP with bilateral chondritis of pinnae and non-erosive polyarthritis. [Methods] The pinna was assessed by longitudinal images. The fingers and wrists were assessed by the dorsal view. [Results] The pinna was thickened. Fibrocartilage was depicted between subcutaneous tissue as three-layer structure; isoechoic area to subcutaneous tissue in the middle of the anechoic or hypoechoic area. Power doppler (PD) signals were dominantly observed in anechoic or hypoechoic area. Synovial thickening with PD signal at the MCP joints were dominantly observed around epiphysis compared to diaphysis. Synovial thickening with PD signal was also observed in the wrists. The hypoechoic thickening of flexor tendon sheathes was observed in the left third finger and the left ECU, with PD signal. [Conclusion] 1) the chondritis of pinna can be detected by US. 2) Synovitis in the vicinity of hyaline cartilage of MCP joints and wrists suggests immune response to cartilaginous tissue in RP. 3) The synovitis of tendon sheath exists in RP. 4) The patient will be observed by US to follow the therapeutic effects.

### P3-023

#### Systematic review of MRI study of osteonecrosis of the femoral head associated with corticosteroid

Junichi Nakamura<sup>1</sup>, Shuichi Miyamoto<sup>1</sup>, Masahiko Suzuki<sup>2</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Graduate School of Medicine, Chiba University, <sup>2</sup>Center for Frontier Medical Engineering, Chiba University

Conflict of interest: None

[Objectives] The purpose of this study was to review the achievement for investigation into pathogenesis of the osteonecrosis of the femoral head associated with corticosteroid by means of the advance of MRI technology in 30 years from its first clinical application. [Methods] Systematic review was performed using Pubmed on January 1<sup>st</sup> 2014. Inclusion criteria were original articles of corticosteroid-associated osteonecrosis of the femoral head using MRI written in English. Articles were divided into three groups by 10 years of published year as follows; 1983-1993, 1994-2003, and 2004-2013. [Results] 145 articles met the above criteria. Number of MRI study increased by decades as follows: 15 articles in 1983 – 1993, 47 in 1994 – 2003, and 83 in 2004 -2013. 44 articles were reported in Japan, 31 in the United States, and 18 in China. 135 articles were clinical research; 68 were retrospective studies, 47 were prospective studies, and 20 were case reports. The remaining 10 were animal studies with MRI in the last decade. The mean impact factor was 2.212 points. [Conclusion] High impact research will be expected for prospective study and basic study of osteonecrosis utilizing MRI.



### P3-024

#### Changes of pulmonary lesions in nontuberculous mycobacterial infection (NTM) with rheumatoid arthritis (RA)

Isamu Yokoe<sup>1</sup>, Atsuma Nishiwaki<sup>1,2</sup>, Hitomi Haraoka<sup>1,2</sup>, Masami Takei<sup>2</sup>  
<sup>1</sup>Itabashi Chuo Medical Center, <sup>2</sup>Division of Hematology and Rheumatology, Nihon University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] To evaluate CT changes of NTM during treatment of RA. [Methods] Twenty-six consecutive RA patients (pts) with suspected NTM were enrolled. CT findings suggesting NTM were 1) centrilobular small granular lesions (CSGL), 2) bronchioloectasis/bronchial wall thickening (B/BWT), 3) cavitation, and 4) small nodules > 5 mm. Sputum culture and follow-up CT were performed every 6 months and some pts also had bronchoscopy. [Results] NTM was diagnosed in 6 pts (*Mycobacterium avium* in 5 and *Mycobacterium abscessus* in 1). All NTM pts had both CSGL and B/BWT. The combination of small nodules and CSGL suggested tuberculosis, while partial B/BWT without CSGL indicated RA lung. All NTM pts were cured by medical therapy, but four pts had exacerbation of RA and received biological products (tocilizumab in 4 and abatacept in 1). B/BWT was usually unchanged, but minimal progression was seen in a few pts. CSGL improved in some pts, but progressed in others. There was no reactivation of NTM, suggesting that these changes were related to RA. [Conclusion] Reactivation of NTM did not occur during treatment of RA. Slight progression of B/BWT may represent the natural history of RA lung. CSGL progressed with exacerbation of RA and care is needed because differentiation from NTM is difficult.

### P3-025

#### Persistence of Extensive MRI Osteitis Associates Rapid Radiographic Progression with Predominance of Joint Space Narrowing Compared with Joint Erosion in Patients with Rheumatoid Arthritis Inadequate Response to Methotrexate

Kou Katayama<sup>1</sup>, Satomi Abe<sup>2</sup>, Tamotsu Kamishima<sup>3</sup>  
<sup>1</sup>Katayama Orthopedic Rheumatology Clinic, <sup>2</sup>Department of Orthopedic Surgery, Asahikawa Medical University, <sup>3</sup>Faculty of Science, Hokkaido University

Conflict of interest: None

[Objectives] To investigate the association of extensive MRI osteitis and RRP and to clarify how joint damage progress with extensive MRI osteitis. [Methods] We compared the clinical and imaging data at the first visit (mean 8.2 months after onset,) and after MTX therapy between one hand with extensive osteitis (osteitis (+)) and another hand with little or no osteitis (osteitis (-)) in 12 RA patients. Gd-enhanced MRI (0.3T) of both hands were evaluated by the RAMRIS. Joint erosion (JE) and joint space narrowing (JSN) score in both hands and feet by the conventional radiography (CR) were also evaluated by the modified total sharp score (m-TSS). Wilcoxon's rank sum test was used to compare continuous data. [Results] The  $\Delta$ mTSS /year and the percentages of the RRP in the first visit (baseline) or after the MTX therapy (about 1year later) were 43.1 and 91.6%, 20.3 and 91.6%, respectively. In osteitis (+) hands, JSN scores in CR significantly increased during MTX therapy ( $P < 0.01$ ) but JE scores did not increased ( $P = 0.25$ ). In osteitis (-) hands, JSN and JE scores in CR did not increased during MTX therapy ( $P < 0.01$ ). [Conclusion] Extensive osteitis is highly associated with RRP. Loss of JSN significantly increased during 1 year MTX therapy ( $P < 0.01$ ) but JE did not increased ( $P = 0.25$ ).

### P3-026

#### Diagnostic utility of ultrasonography in carpal tunnel syndrome: a comparison between RA and non-RA patients

Keita Fujikawa<sup>1</sup>, Akinari Mizokami<sup>1</sup>, Shin-ya Kawashiri<sup>2</sup>, Atsushi Kawakami<sup>2</sup>

<sup>1</sup>Department of Rheumatology, Japan Community Health Care Organization, Isahaya General Hospital, Isahaya, Japan, <sup>2</sup>Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan

Conflict of interest: None

[Objectives] To compare the utility of ultrasonography for diagnosing carpal tunnel syndrome (CTS) in patients with and without rheumatoid arthritis (RA). [Methods] Seventeen patients with CTS were enrolled. Eighteen wrists of RA patient with CTS (RA+CTS), 12 wrists of CTS patient without RA (non-RA+CTS), 42 wrists of RA patient without CTS (RA control) and 26 wrists of healthy subjects (healthy control) were assessed in ultrasonography. We evaluated maximum and minimum value of cross-sectional area (CSA) and power Doppler (PD) signal in median nerve, and tenosynovitis of flexor tendon. [Results] CSA of the median nerves were significantly higher in the CTS patients compared with the RA and healthy controls. Receiver operating characteristics (ROC) analysis revealed that maximum value of CSA  $\geq 12\text{mm}^2$  was the most powerful predictor of CTS patients (AUC=0.93; sensitivity 87%, specificity 90%). The frequency of the patients with PD signal in median nerve and tenosynovitis of flexor tendon were significantly higher in the RA+CTS patients compared with the non-RA+CTS patients. [Conclusion] CSA measurement of median nerve in ultrasonography is useful for the diagnosis of CTS. This study suggest that tenosynovitis of flexor tendon induce compression of median nerve in RA patients

### P3-027

#### Ultrasonography in the detection of foot and ankle synovitis in rheumatoid arthritis

Takeshi Kashiwagura<sup>1</sup>, Seiya Miyamoto<sup>2</sup>, Masakazu Urayama<sup>4</sup>, Moto Kobayashi<sup>5</sup>, Toshiaki Aizawa<sup>6</sup>, Hiroshi Aonuma<sup>7</sup>, Yusuke Sugimura<sup>3,8</sup>, Naohisa Miyakoshi<sup>8</sup>, Yoichi Shimada<sup>8</sup>

<sup>1</sup>Department of Rehabilitation Medicine, Akita City Hospital, Akita, Japan, <sup>2</sup>Department of Orthopedic Surgery, Nakadori General Hospital, Akita, Japan, <sup>3</sup>South Akita Orthopedic Clinic, Akita, Japan, <sup>4</sup>Department of Orthopedic Surgery, Ogachi Central Hospital, Akita, Japan, <sup>5</sup>Department of Orthopedic Surgery, Hiraka General Hospital, Akita, Japan, <sup>6</sup>Department of Orthopedic Surgery, Kita Akita Municipal Hospital, Akita, Japan, <sup>7</sup>Department of Orthopedic Surgery, Kakunodate Municipal Hospital, Akita, Japan, <sup>8</sup>Department of Orthopedic Surgery, Akita University Graduate School of Medicine, Akita, Japan

Conflict of interest: None

[Background] Rheumatoid arthritis (RA) can cause various types of foot and ankle deformities. Although joint ultrasonography is frequently used for the evaluation of disease activity in RA, few studies have used it for the joints of the foot and ankle. [Objective] We aimed to assess the prevalence of foot and ankle synovitis in RA patients using joint ultrasonography. [Methods] Sixty patients (18 men and 42 women) with 82 feet took part in the study. The 15 scanned areas included in this study. [Results] Synovitis of the foot or ankle was detected in 49 of 82 feet (59.8%). It was observed in 78.3% of the patients with moderate to high disease activity scores, as well as 44.7% of those with low disease activity. Even among patients without foot complaints, synovitis was present in 22 of 49 feet (44.9%). [Discussion] This study found a high prevalence of synovitis of the foot and ankle in RA patients irrespective of the presence or absence of symptoms or the degree of disease activity. We propose that RA patients with persistent synovitis may be candidates for further treatment, and clinicians should consider additional pharmacotherapy to prevent joint destruction. For selected patients with foot and ankle synovitis, synovectomy of small joints may be beneficial.

### P3-028

#### Capillaroscopic Examination of Capillary Disorder in Patients with Rheumatic Disease

Satoshi Suzuki<sup>1,2</sup>, Souichiro Nakano<sup>1,2</sup>, Toshio Kawamoto<sup>2</sup>, Ran Matsudaira<sup>2</sup>, Yoshinori Kanai<sup>2</sup>, Kenjiro Yamanaka<sup>2</sup>, Yoshinari Takasaki<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, <sup>2</sup>Department of Internal Medicine and Rheumatology, Sasaki Institute Kyoundo Hospital

Conflict of interest: None

[Introduction] Rheumatic disease (RD) is known to cause impairment of microvascular blood flow and various damages. Rheumatologists have focused attention on the importance of capillary disorder; however, abnormal capillary findings have not been used in the diagnosis of RD. The

nail folds are known to be suitable sites for assessment of capillaries. Recently, nailfold capillaroscopy was developed to assess nailfold capillaries and has enabled detailed analysis of capillary morphology. [Methods] Patients with RD who visited Kyoundo Hospital, between October 2012 and January 2013 were included in this study. The results were verified based on the diagnosis, medical history, autoantibodies, and treatment administered. [Results] Nailfold capillaries in patients with RD other than primary Raynaud's syndrome or scleroderma were likely to maintain normal function regardless of disease duration. However, abnormal nailfold capillaries were observed early in patients with scleroderma. [Conclusion] Assessment of nailfold capillaries may facilitate early screening for scleroderma. Moreover, examination of scleroderma-specific patterns would allow not only the assessment of disease stage but also the prediction of complications.

### P3-029

#### **A Treatment of Acute Calcific tendinitis of the longus colli muscle, Report of Seven Cases**

Tsutomu Sakuraba<sup>1</sup>, Takeshi Kashiwagura<sup>2</sup>, Yusuke Sugimura<sup>3</sup>, Seiya Miyamoto<sup>4</sup>, Naohisa Miyakoshi<sup>5</sup>, Yoichi Shimada<sup>5</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Hiraka General Hospital, <sup>2</sup>Department of Rehabilitation Medicine, Akita City Hospital, <sup>3</sup>South Akita Orthopedic Clinic, Akita, Japan, <sup>4</sup>Department of Orthopedic Surgery, Nakadori General Hospital, Akita, Japan, <sup>5</sup>Department of Orthopaedic Surgery, Akita University Graduate School of Medicine

Conflict of interest: None

[Objective] In the recent years, the cases of Acute Calcific tendinitis of the longus colli muscle have been reported as a cause of an acute neck pain analogous with Crowned Dens syndrome (CDS). About the seven cases we experienced, we present here to make a comparative review. [Materials] Between 2009 and 2014, we treated 7 patients; four men and three women. Except for a patient coexisting CDS, all cases were in thirties and forties. Seven cases had acute neck pain and stiffness, of whom three patients also experienced dysphagia. The symptoms were resolved in 1 to 2 weeks treated with anti-inflammatory and analgesic medications. [Discussion] The clinical condition is caused by an inflammation with the deposition of hydroxyapatite crystals in the superior oblique tendon fibers of the muscle. In comparison to CDS, the calcification in CT was sharply-margined, round and the age of onset was earlier. This must be differentiated from pharyngitis, retropharyngeal abscess and purulent spondylitis. Detection in the front of Axis (C2) and swelling of the retropharyngeal space is very important for a diagnosis. [Conclusion] An increased awareness of disease will result in improved early diagnosis and can prevent misdiagnosis with inappropriate interventions such as surgical drainage.

### P3-030

#### **A case of monoarthritis in rheumatic fever evaluated with musculoskeletal ultrasound sonography**

Tomoyuki Asano, Hiroko Kobayashi, Makiko Yashiro, Naoki Matsuoka, Shuzo Sato, Hiroshi Watanabe, Hiromasa Ohira  
Department of Gastroenterology and Rheumatology, School of Medicine, Fukushima Medical University

Conflict of interest: None

Case: In 2009, a 36-year-old man suffered arthralgia subsequent to sore throat. After a month later, he fell into severe heart failure with mitral and aortic valve regurgitation. For a *Streptococcus* was positive in blood culture test, he had a diagnosis of rheumatic fever (RF). After prosthetic valve replacement surgery, heart failure state was improved. However, arthritis of his left elbow had been prolonged for 4 years despite the treatment with prednisolone. In 2013, he was referred to our department and musculoskeletal ultrasound sonography (MSUS) was performed. MSUS revealed severe synovial thickening and positive signal of Power Doppler in his left elbow. These findings seemed similar to those of rheumatoid arthritis (RA). After treatment of amoxicillin, his symptom was alleviated. A month later, MSUS revealed significant reduction of synovial thickening and signal of Power Doppler. Discussion: So far no report regarding arthritis in RF evaluated with MSUS has been described. In

previous histopathological report about RF joint, neutrophil infiltration in synovial fluid and lymphocytes or plasma cells infiltration in synovium were found, which were similar to those of RA (*Syrmens, Systemic Pathology 1979*). From this report, our case may represent typical RF feature with MSUS.

### P3-031

#### **Bone erosion was observed in a patient of RA whose inflammatory reaction is normal range**

Koichiro Satoh  
Fukushima Medical University

Conflict of interest: None

[Objectives] The evaluation of the bone change was excluded from the 2010 ACR-EULAR classification criteria. The bone lesion of the case that I cannot classify as RA in the new criteria may actually progress to be RA. [Methods] I introduce an out-patient who is visiting to our hospital from 2005. Female. She is 36 years old now. Chief Complaints are left knee pain and IP joint pain of right thumb. CRP 0.8mg/dl, BSR 8mm/1H, RF 25. I could not confirm bone erosion in her hands of X-ray. On the other hand, we could observe the hyperostosis in her X-ray. Then we thought she has some arthritis. We started to treat her by 500mg/day of SASP. CRP 0.1mg/dl, BSR 7mm/1H, RF 20, MMP-3 116 in September, 2008. We confirmed her bone erosion of her right hand of X-ray in December, 2008. Then I have an X-ray examination evidence of the progression of bone change. We added MTX to treat her arthritis. Now, CRP <0.03mg/dl, BSR 3mm/1H, RF 22, MMP-3 38.9. X-ray indicated narrowing of her right wrist, bone erosion of her lunate and left ulnar head. [Results] RA progressing bone erosion exist. even if we can not confirm the state of inflammatory reaction in RA patients in serum examination. [Conclusion] I emphasize that X-rays evaluation should be excluded from a classification and an evaluation of RA

### P3-032

#### **Characteristics of elder patients of rheumatoid arthritis in *NinJa* data bases of 2008 and 2013**

Shigeru Yoshizawa<sup>1</sup>, Kyoko Yoshihiro<sup>1</sup>, Toshihiro Matsui<sup>2</sup>, Shigeto Tohma<sup>3</sup>  
<sup>1</sup>Department of Rheumatology, Fukuoka National Hospital, National Hospital Organization, Fukuoka, Japan, <sup>2</sup>Department of Rheumatology, Sagami National Hospital, National Hospital Organization, Kanagawa, Japan, <sup>3</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, National Hospital Organization, Kanagawa, Japan

Conflict of interest: None

[Objectives] To estimate the latest characteristics of elder patients of rheumatoid arthritis (RA) in the data base of *NinJa* 2013, the disease activity and the medication of the patients of elder than 75 years old were compared to those of *NinJa* 2008. [Methods] To avoid the influence of the disease duration of RA, the groups of the patients of less than two years disease duration in both *NinJa*2008 (996 patients) and *NinJa* 2013 (2747 patients) were examined. [Results] The ratio of the patients in remission and in low disease activity by DAS28-ESR was 23.6% and 15.7% in *NinJa* 2008, whereas 32.6% and 18.0% in *NinJa*2013, respectively. The ratio of the patients of MTX administration were 24.3% in *NinJa* 2008, and 47.4% in *NinJa* 2013, and those of biologic DMARDs were 2.8% and 12.4%, respectively. The ratio of administration of glucocorticoid decreased from 68.3% in *NinJa* 2008 to 47.2% in *NinJa* 2013. [Conclusion] The disease activity of elderly patients of RA in data base of *NinJa* 2013 were more controlled than in that of 2008, because MTX and biologic DMARDs were more aggressively given to the elder RA patients in *NinJa* 2013 than that in *NinJa* 2008.

### P3-033

#### **Overproduction of MMP-3 may be involved in the complication of interstitial lung disease in rheumatoid arthritis**

Toshie Higuchi<sup>1</sup>, Ayumi Uchino<sup>2</sup>, Toshiyuki Ota<sup>2</sup>, Shuji Nagano<sup>2</sup>, Yoshinobu Koyama<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Center for Autoimmune Diseases, Japa-

nese Red Cross Okayama Hospital, <sup>2</sup>Department of Rheumatology, Center for Rheumatology, Iizuka Hospital

Conflict of interest: None

[Objectives] To define the involved factors for the pathogenesis of interstitial lung disease (ILD) in rheumatoid arthritis (RA), association of the decreased DLCO with the disease activity score (DAS) or the data of laboratory findings were investigated. [Subjects & Methods] The 115 of treatment-naïve-RA patients were included in this study. The %DLCO as an indicator of ILD was evaluated in two hospitals. As it might be a problem to combine the raw data of %DLCO measured in two facilities, standardized values were applied for the investigation. The difference in the DAS and the laboratory findings (ESR, CRP, MMP-3, SAA, RF, ACPA) between “suspected ILD” group (%DLCO<50) and “normal” group (%DLCO>50) were investigated. [Results] No significant differences were found in RF, ACPA, SAA or CRP between these groups. Although ESR was significantly higher in “suspected ILD” group (P=0.0025), no significant differences were found in DAS-ESR. The values of MMP-3 were also significantly higher in ILD group (p=0.0010). [Conclusion] The serum MMP-3 seemed to be the most significant item if “suspected ILD” with “normal” group was compared. The finding supports the hypothesis that the overproduction of MMP-3 may be involved in the pathogenesis of ILD in RA

### P3-034

#### **In the examination of each association between anti CCP antibody and a rheumatoid factor (RAPA) and some inflammatory markers and a serum iron, we suggest a hybrid mechanism of inflammation in rheumatoid arthritis. (RA)**

Kazuo Jouyama, Tomoyuki Mutoh, Yousuke Murata, Naoya Sawada, Akihiro Yamada, Kenichiro Matoba, Makoto Onishi, Yasuaki Okuda, Kiyoshi Takasugi

Center for Rheumatic Disease, Dohgo Spa Hospital, Ehime, Japan

Conflict of interest: None

[Objectives] We suggest a mechanism of inflammation in RA. [Methods] The retrospective study of 202 patients with RA to meet the ACR classification criteria in 1987. We divided those into 4 groups for positive or negative of anti CCP antibody and RAPA and evaluated CRP, MMP-3, Granulocyte, Gamma globulin and divided those into 3 groups by an anti CCP antibody level and evaluated, as for RAPA similarly and examined each association between the reciprocal of the serum iron (equivalent to IL -6) and 4 inflammatory markers, anti-CCP antibody, RAPA. [Results] Anti CCP antibody and RAPA with CRP, MMP-3, Granulocyte was unrelated but was related to Gamma globulin synergistically. The reciprocal of the serum iron was related to CRP, MMP-3, Gamma globulin, anti CCP antibody, RAPA and by the multiple regression analysis predicting the reciprocal, CRP and MMP-3 were main explanation factors. [Conclusion] We suggest a hybrid mechanism of inflammation in RA. One is the innate immunity by environmental factors, associated with CRP, MMP-3, Granulocyte, causes acute inflammation mainly on IL-6. Another is adaptive immunity with the genetic predisposition, such as anti CCP antibody, RAPA, Gamma globulin, causes chronic inflammation and exacerbates inflammation continuously and worsens a prognosis.

### P3-035

#### **Seropositivity of rheumatoid factor and anti-citrullinated protein antibody in joint surgeries for patients with rheumatoid arthritis**

Shinichi Mizuki, Kazuhiko Higashioka, Kenji Yoshida, Kensuke Oryoji, Kazuo Kamada, Eisuke Yokota

The Centre for Rheumatic Diseases, Matsuyama Red Cross Hospital

Conflict of interest: None

[Objectives] To investigate the role of rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) positivity as a contributor to the orthopedic surgeries for rheumatoid arthritis (RA) patients. [Methods] The study examined orthopedic data from our center (1980-) with linkage to RF/ACPA data set of our hospital. Patients were categorized

into the following four groups: double-negative (RF-/ACPA-), RF-/ACPA+, RF+/ACP- and double-positive (RF+/ACP+). [Results] A total of 440 orthopedic surgical procedures in 241 patients were analyzed. Most of the patients (83.4%) were double positive, 8.3% were RF+/ACPA-, 5.3% were RF-/ACPA+ and 2.9% were double negative. Although similar percentage was observed in patients with RF+/ACPA- and RF-/ACPA+ in procedures for large joints (elbow, hip, knee and ankle), higher percentage (8.3%) was in RF+/ACPA- than in RF-/ACPA+(3.3%) in small joints (hand and forefoot) surgeries. [Conclusion] The combined presence of RF and ACPA is associated with orthopedic surgeries. Our data suggest that RF may contribute to RA joint destruction regardless of the presence of ACPA.

### P3-036

#### **A cross-sectional analysis of wrist and forefoot deformities in rheumatoid arthritis -- KURAMA cohort~**

Yosuke Hamamoto<sup>1</sup>, Hiromu Ito<sup>1</sup>, Moritoshi Furu<sup>2</sup>, Motomu Hashimoto<sup>2</sup>, Takao Fujii<sup>2,3</sup>, Noriyuki Yamakawa<sup>3</sup>, Chikashi Terao<sup>4</sup>, Masahiro Ishikawa<sup>2</sup>, Hiroko Ogino<sup>1</sup>, Takahiro Iwata<sup>1</sup>, Masayuki Azukizawa<sup>1</sup>, Tsuneyo Mimori<sup>2,3</sup>, Shuichi Matsuda<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan, <sup>2</sup>Department of the Control for Rheumatic Diseases, Graduate School of Medicine, Kyoto University, Kyoto, Japan, <sup>3</sup>Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan, <sup>4</sup>Department of the Center for Genomic Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Conflict of interest: None

[Objectives] Forefoot and wrist are the most-frequently deformed joints in rheumatoid arthritis (RA). However, it is not well understood that the frequency, degree and effects on ADL of these deformities. We investigated the frequency and impact using the KURAMA cohort which was a large-scale cohort. [Methods] In the RA patients who enrolled in KURAMA cohort, we investigated in 370 patients (average age; 62.9 years old, female ratio; 87.6%). We conducted a statistical evaluation about the association between radiographic index (wrist and toe MTP joint Larsen grade) and demographic data such as age, sex, duration of the disease, disease activity and the functional index. [Results] To the wrist joint has all of foot Larsen grade correlation. but there were no correlations with age, sex, medication contents and the disease activity at the time of investigation. It tended to be seen many people of foot deformation in morbidity early. [Conclusion] It is considerably high in the frequency of the forefoot deformities in RA and correlates with duration of the disease.

### P3-037

#### **Significance of patient global assessment in rheumatoid arthritis patients**

Norikazu Hirano

Toyama Rousai Hospital, Toyama, Japan

Conflict of interest: None

[Objectives] Patient global assessment (PtGA) is a pure subjective evaluation of each patient with rheumatoid arthritis, so often different from the objective findings. Significance of PtGA was examined by the statistical analysis. [Method] PtGA and other 16 objective items were recorded from 71 patients with rheumatoid arthritis. Sixteen objective items were sex, age, stage and class of Steinbrocker, treatment years, swollen joint count, tender joint count, ESR, CRP, mHAQ, and the presence or absence of a therapeutic agent (csDMARD, methotrexate, bDMARD, steroid, non-steroidal anti-inflammatory drug (NSAID), and tacrolimus). Quantification theory I (Hayashi) was performed. Multiple correlation coefficient, contribution ratio, partial correlation coefficient of 16 items, and the category quantity in each item were calculated. [Result] The multiple correlation coefficient was 0.88, and the contribution rate was 0.78. These results meant that 78% of the change in PtGA could be explained by the 16 items. Partial correlation coefficients with significant value were 0.47 of csDMARD, 0.45 of mHAQ, 0.42 of class of Steinbrocker, 0.42 of NSAID. [Conclusion] PtGA is mainly reflected

success of csDMARD therapy, the degree of restriction of daily life, and the pain.

### P3-038

#### Relevance of P-glycoprotein (P-gp) expression on CXCR5<sup>+</sup>CD4<sup>+</sup>T cells to inflammatory manifestation in highly active rheumatoid arthritis

Shizuyo Tsujimura, Kazuyoshi Saito, Shingo Nakayamada, Yoshiya Tanaka

The First Department of Internal Medicine, University of Occupational & Environmental Health, Japan

Conflict of interest: None

[Objectives] P-gp on activated lymphocytes in active RA patients leads to P-gp-mediated multidrug resistance due to efflux of intracellular drugs. In our previously investigation, CXCR5<sup>+</sup>CD4<sup>+</sup>T cells, that promote antibody production from B cell, were increased in RA patients. The aim of this study is evaluate the relevance of P-gp and CXCR5 expression on CD4<sup>+</sup>T cells to tissue inflammation in RA. [Methods] Lymphocytes were analyzed using Immunohistochemistry and flow cytometry. [Results] P-gp expression was preferentially high on CXCR5<sup>+</sup>CD4<sup>+</sup>T cells. P-gp expression level on CXCR5<sup>+</sup>CD4<sup>+</sup>T cells, but not CXCR5 on CD4<sup>+</sup>T cells, correlated with SDAI. Accumulation of P-gp<sup>+</sup>CXCR5<sup>+</sup>CD4<sup>+</sup>T cells and P-gp<sup>+</sup>B cells was noted in inflammatory lesions of synovitis and interstitial pneumonia. Active RA patients with severe extra-articular involvement showed expansion of both P-gp<sup>+</sup>CXCR5<sup>+</sup>CD4<sup>+</sup>T and P-gp<sup>+</sup>B cells. Reduction in P-gp<sup>+</sup>CXCR5<sup>+</sup>CD4<sup>+</sup>T cells and P-gp<sup>+</sup>B cells by combination therapy including adalimumab was resulted in recovery of intracellular drug levels in lymphocytes and following improvement of organ involvement. [Conclusion] Local accumulation of P-gp<sup>+</sup>CXCR5<sup>+</sup>CD4<sup>+</sup>T cells in inflamed tissue might be involved in enhancement articular and extra-articular tissue damage.

### P3-039

#### Analysis of the control mechanism of Th17 cell differentiation by T-bet

Masahiro Yokosawa, Yuya Kondo, Masahiro Tahara, Shunta Kaneko, Seiji Segawa, Hiroto Tsuboi, Isao Matsumoto, Takayuki Sumida  
Department of Internal Medicine, Faculty of Medicine, University of Tsukuba

Conflict of interest: None

[Objectives] The differentiation of Th subsets are determined by the expression of each specific transcription factors. This study was intended to clarify the control mechanism of the Th-17 cell differentiation by Th-1 specific transcription, T-bet. [Methods] 1) CD4<sup>+</sup> T cells from B6, T-bet transgenic (Tg) mice, and Tg/IFN $\gamma$ <sup>-/-</sup> mice were cultured for Th-17 cell differentiation, then the ROR $\gamma$ t expression, IL-17 production, and transmission mechanism of the related signal were analyzed by flowcytometry. 2) Naïve CD4<sup>+</sup> T cells from B6 were transduced T-bet gene with retrovirus vector, and the cells were cultured for Th-17 cell differentiation, then the ROR $\gamma$ t expression and IL-17 production were analyzed by flowcytometry. [Results] 1) The IL-17 production was suppressed in Tg mice and Tg/IFN $\gamma$ <sup>-/-</sup> mice compared with B6 mice. Phosphorylation of STAT3 by IL-6 stimulation was also inhibited in Tg mice and Tg/IFN $\gamma$ <sup>-/-</sup> mice. 2) ROR $\gamma$ t expression and IL-17 production were suppressed by the transduction of T-bet gene to naïve CD4<sup>+</sup> T cells. [Conclusion] This study suggested the possibility that T-bet regulates the differentiation of Th-17 cells via the inhibition of STAT3 phosphorylation independent of IFN $\gamma$  that had not previously pointed out.

### P3-040

#### Results of Multi-center Rheumatoid Arthritis (RA) Patient Survey (4) Thoughts regarding injections

Tsukasa Matsubara<sup>1,2</sup>, Hiroaki Matsuno<sup>1</sup>, Keiko Funahashi<sup>2</sup>, Yosuke Nishioka<sup>1</sup>, Tamami Yoshitama<sup>1</sup>, Norihiko Koido<sup>1</sup>, Masakazu Kondo<sup>1</sup>, Tomohiko Yoshida<sup>1</sup>, Yoshiki Shiohira<sup>1</sup>, Kenji Mannami<sup>1</sup>, Masaaki Yoshida<sup>1</sup>, Hideshi Yamazaki<sup>1</sup>, Katsuhiko Narushima<sup>1</sup>, Yasuhiko Hirabayashi<sup>1</sup>, Toyomitsu Tsuchida<sup>1</sup>, Masato Okada<sup>1</sup>, Takehiko Ayabe<sup>1</sup>, Atsuko Imai<sup>1</sup>, Yasuhiko Munakata<sup>1</sup>, Tatsuo Kotsuma<sup>1</sup>, Kazuyasu Ushio<sup>1</sup>,

Shuji Abe<sup>1</sup>, Hideo Kagawa<sup>1</sup>, Takeshi Mitsuka<sup>1</sup>, Jiro Yamana<sup>1</sup>, Shinichi Ishioka<sup>1</sup>, Chiyuki Abe<sup>1</sup>

<sup>1</sup>Japanese Clinician's Biologic Research Group, <sup>2</sup>Matsubara Mayflower Hospital

Conflict of interest: Yes

[Objectives]7 biologics can now be utilized and development continues. Self-injected BIO have been available for 9 years, and treatment with oral medications that match BIO is now possible, but patient opinion regarding self-injection is not clear. A multi-center survey was done. [Methods] Written consent and background from 9437 patients at 51 facilities. Patients were polled on subcutaneous injections (SC) vs. IV injections (IV). Results were calculated for the BIO experience (BG) and DMARDS group (DG). [Results] Patient data- 83% female, disease duration 10-20 years, age average in the 50s. For self-injected SC, 43% of BG chose 'convenient' vs. 14% of DG. 33% of BG and 55% of DG responded 'do not want to'. For SC at hospital, the numbers who chose 'convenient' were higher, 62% and 47% respectively. As for IV injections, 54% of BG group chose 'convenient', and 38% of DG 'do not want to'. Regardless of area, about half of all patients deemed in-hospital SC 'convenient', and a quarter self-injected SC as 'convenient'. On the other hand, differences were seen towards IV injections. [Conclusion] For RA patients, in-hospital SC was seen as most convenient, but the authors propose that with education patients are likely to accept self-injection. Attitudes towards IV injections differed.

### P3-041

#### Comparison of treatment outcome, among age of onset in rheumatoid arthritis patient

Akitoshi Maeda, Yoshiaki Kusaka

Murakami Memorial Hospital, Asahi University, Gifu, Japan

Conflict of interest: None

[Objectives] To compare the treatment outcome of rheumatoid arthritis patients among age, that was treated within 6 months after onset. [Methods] We retrospectively compared treatment outcome between ages of onset in rheumatoid arthritis patients. Cases were treated within 6months after onset and now treated our facility. We grouped cases, disease onset younger than 65 years old "Y", onset 65 years or older "E". [Results] There were 8 cases in Y, 14 cases in E. The mean age of onset was 51.5 years old for Y, 74.1 years old for E. Female were 5 (62.5%) in Y and 8 (57.1%) in E. One year after treatment started, MTX were used in 5 (62.5%) cases in Y, 8 (28.6%) cases in E. Mean amount of MTX used were 8.4mg/week, 5.0mg/week. One year after treatment started, PSL were used in 3 (37.5%) cases for Y, 9 (64.3%) cases for E. Mean measurement of CRP before treatment was 4.25 for Y, 3.39 for E which both lowered to 0.09 and 0.22 one year after treatment. Mean DAS28-ESR after a year of treatment was 2.04 for Y, 2.25 for E. Remission was achieved in 7 (87.5%) cases in Y, 9 (64.3%) cases in E. Including low disease activity, 8 (100%) cases and 11 (78.6%) cases were so. [Conclusion] Regardless of age, good treatment outcome were achieved. For the elderly less MTX and more PSL were used.

### P3-042

#### Patient satisfaction is most correlated with patient global assessment and role of QOL in patients with rheumatoid arthritis

Mie Fusama<sup>1,4</sup>, Kumiko Yukioka<sup>2</sup>, Takanori Kuroiwa<sup>2</sup>, Chikako Yukioka<sup>2</sup>, Miyako Inoue<sup>2</sup>, Tae Nakanishi<sup>2</sup>, Norikazu Murata<sup>2</sup>, Noriko Takai<sup>2</sup>, Kayoko Higashi<sup>1</sup>, Taro Kuritani<sup>3</sup>, Keiji Maeda<sup>3</sup>, Yasushi Miura<sup>2</sup>, Hajime Sano<sup>5</sup>, Masao Yukioka<sup>2</sup>, Hideko Nakahara<sup>3,6</sup>

<sup>1</sup>Division of Nursing, NTT West Osaka Hospital, <sup>2</sup>Yukioka Hospital, <sup>3</sup>Division of Allergy, Rheumatology and Connective Tissue Diseases, Department of Internal Medicine, NTT West Osaka Hospital, <sup>4</sup>Kobe University Graduate School of Health Sciences, <sup>5</sup>Hyogo College of Medicine, <sup>6</sup>Kansai Health Administration Center, NTT West Corporation

Conflict of interest: None

[Objective] We evaluated which factor is correlated with patient satisfaction in patients with RA. [Method] Patient satisfaction was assessed

with patient satisfactory scores of AIMS-2. Correlation was evaluated with SJC, TJC, PGA, EGA and Pain-VAS. Psychological factors and QOL were also examined utilizing STAI and CES-D and 5 scores of AIMS-2, respectively. Data analyses were performed using Spearman correlation analysis. [Results] The patients with RA (n=112) were recruited. There is no statistically significant correlations between satisfaction and age or duration. Regarding disease activity, satisfaction was most correlated with PGA (r=0.603) followed by Pain-VAS (r=0.5595) and TJC (r=0.4585) (all, p<0.0001), while weakly correlated with EGA and SJC. STAI (State) (r=0.4419) and CES-D (r=0.4357) were moderately correlated with satisfaction (both, p<0.0001), while no statistically significant correlation was shown between satisfaction and STAI (Trait). In 5 scores of AIMS-2, satisfaction is strongly correlated with role (r=0.7081) followed by affect (r=0.6916), physical score (r=0.6695) and symptom (r=0.6259) (all, p<0.0001), while weakly correlated with social function. [Conclusion] Patient satisfaction was most correlated with PGA and role in QOL in patients with RA.

### P3-043

#### Identification of a factor predicting response to tocilizumab as treatment for rheumatoid arthritis

Satoshi Suzuki<sup>1,2</sup>, Souichiro Nakano<sup>1,2</sup>, Seiichiro Ando<sup>2</sup>, Ran Matsudaira<sup>1</sup>, Yoshinori Kanai<sup>1</sup>, Kenjiro Yamanaka<sup>1</sup>, Yoshinari Takasaki<sup>2</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Sasaki Institute Kyoundo Hospital, <sup>2</sup>Department of Internal Medicine and Rheumatology, Juntendo University

Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) patients frequently have concomitant anemia. In this study, we focused on determining the underlying mechanism of action of tocilizumab in improving anemia in chronic inflammation by directly inhibiting signaling via IL-6 receptors. [Methods] Serum levels of hepcidin-25, expression of which is IL-6 dependent and a major cause of anemia in chronic inflammation, was measured in the serum of 10 patients before and after tocilizumab administration. We compared variations in the levels of various inflammatory cytokines and clinical data to determine whether these factors might predict response to tocilizumab. [Results] Serum hepcidin-25 levels were elevated in most of the RA patients and decreased after tocilizumab administration. In tocilizumab non-responders, however, serum hepcidin-25 levels were normal or low and increased after administration. Moreover, in non-responders, serum IL-6 levels also tended to be either low or abnormally high before administration. [Conclusion] Hepcidin-25 levels may be helpful in predicting response to tocilizumab.

### P3-044

#### Correlation of adherence with psychological state in patients with rheumatoid arthritis

Miyako Inoue<sup>1</sup>, Hideko Nakahara<sup>2</sup>, Mie Fusama<sup>2</sup>, Chikako Yukioka<sup>1</sup>, Takanori Kuroiwa<sup>1</sup>, Sayuri Arimitsu<sup>1</sup>, Kumiko Kobayashi<sup>1</sup>, Jin Sawada<sup>1</sup>, Futoshi Yukioka<sup>3</sup>, Tae Nakanishi<sup>1</sup>, Keiji Maeda<sup>2</sup>, Norikazu Murata<sup>1</sup>, Suguru Osawa<sup>1</sup>, Kumiko Yukioka<sup>1</sup>, Masao Yukioka<sup>1</sup>

<sup>1</sup>Yukioka Hospital, <sup>2</sup>NTT West Osaka Hospital, <sup>3</sup>Hyogo College of Medicine

Conflict of interest: None

[Objectives] We evaluate correlation of adherence with psychological state in patients with rheumatoid arthritis (RA) [Methods] Assessment of psychological state was performed utilizing CES-D, a measure evaluating depression. Adherence was evaluated utilizing Adherence Starts with Knowledge (ask)-12. The patients with RA were divided to depression group (CES-D≥16) and non-depression group (CES-D<16). Adherence was compared between depression group and non-depression group. [Results] Twenty-one patients (3 males and 18 females) were enrolled. Average age: 54.4 years. Average disease duration: 16.6 years. Eight patients (38.1%) were in depression group. There is no significant difference in age, duration, Class, Stage and CDAI between depression group and non-depression group. No significant difference was also found in dosages of prednisolone and methotrexate. The adherence of depression group was significantly lower compared with that of non-depression

group (p=0.0168). [Conclusion] The patients with depression are significantly higher in adherence compared with patients with non-depression. This result suggests psychological support might to be effective to improvement adherence.

### P3-045

#### Anxiety and depression in patients with rheumatoid arthritis (RA) who consulted our hospital for the first time

Chikako Yukioka<sup>1</sup>, Masao Yukioka<sup>1</sup>, Sayuri Arimitsu<sup>1</sup>, Norikazu Murata<sup>1</sup>, Suguru Osawa<sup>1</sup>, Takanori Kuroiwa<sup>1</sup>, Hideko Nakahara<sup>2</sup>, Mie Fusama<sup>2</sup>, Kenji Miki<sup>3</sup>, Kenrin Shi<sup>4</sup>, Makoto Hirao<sup>4</sup>, Kosuke Ebina<sup>4</sup>

<sup>1</sup>Yukioka Hospital, Osaka, Japan, <sup>2</sup>Nippon Telegraph and Telephone West Corporation Osaka Hospital, Osaka, Japan, <sup>3</sup>Kinki University, Osaka, Japan, <sup>4</sup>Osaka University, Osaka, Japan

Conflict of interest: None

[Objectives] We investigated the incidence of a depressive state in patients with RA on the initial consultation, as well as the association between depression and pain/functional disorder/anxiety. [Methods] The subjects were 112 patients with RA who consulted our hospital for the first time, and could be surveyed between February 2008 and November 1, 2013 (17 males, 95 females), with a mean age of 56 years at the time of this survey. Using a simple depression-evaluating test (CES-D), we evaluated the depressive state, and investigated VAS, MHAQ and state/trait anxiety using STAI with respect to the presence or absence of depression. [Results] In patients with depression, the VAS, MHAQ, and MHAQ for the upper limbs, state anxiety, trait anxiety, and face scale were significantly higher than in those without it. The degree of satisfaction with (sleep VAS) was lower. There was a significant difference in the MHAQ for the upper limbs, but there was no significant difference in that for the lower limbs. There were also no significant differences in the class, BSG, CRP, RF, MMP3, anti-CCP antibody blood serotonin. [Conclusion] In RA patients with depression, pain and functional disorder deteriorate. In contrast, these factors may induce the patient's depressive state and anxiety, affecting their quality of life (QOL).

### P3-046

#### Effectiveness of life extension in elderly rheumatoid arthritis patients treated with biologics

Kazuhiro Fukuoka, Miho Karube, Noriko Ikegaya, Hideki Shimizu, Satoshi Hayakawa, Yoshinori Komagata, Shinya Kaname, Yoshihiro Arimura

1st Internal Medicine, division of Rheumatology and Nephrology, Kyorin University School of Medicine

Conflict of interest: None

[Objectives] Our purpose is define whether the biologics treatment has an effect of life extension in elderly RA or not, then clarify the predict factors of severe complications. [Methods]his study was single mono-center retrospective observation study. We analyzed RA cases treated with in our hospital from 2010 to 2013. Subjects were divided into the biologics group and non-biologic groups, (matched in ages), and compare the life span, and frequency of severe complication. [Results] All RA cases we analyzed were 1,440, the percentage of the biologics group was 25.5%. There was no significant difference in the life span in these two groups, and the frequency of admission also did not show the significant differences. Duration of RA, the total dosage of immune-suppressant, and past history were shown as the risk factor for admission. [Conclusion] For the improvement of QOL, biologic treatment is also useful in elderly RA cases.

### P3-047

#### Results of Multi-center Rheumatoid Arthritis (RA) Patient Survey (3) Treatment costs and time factors

Hiroaki Matsuno<sup>1</sup>, Tsukasa Matsubara<sup>1,2</sup>, Keiko Funahashi<sup>2</sup>, Akira Sagawa<sup>1</sup>, Tomomaro Izumihara<sup>1</sup>, Masanori Adachi<sup>1</sup>, Mitsuhiro Iwahashi<sup>1</sup>, Tetsu Oyama<sup>1</sup>, Yuichi Nishioka<sup>1</sup>, Keisuke Hashimoto<sup>1</sup>, Motohiro Oribe<sup>1</sup>, Yuichi Takahashi<sup>1</sup>, Kensuke Kume<sup>1</sup>, Eisuke Shono<sup>1</sup>, Takaki Nojima<sup>1</sup>, Nobumasa Miyake<sup>1</sup>, Akihiko Nakamura<sup>1</sup>, Takefumi Kato<sup>1</sup>, Eiji Otsuka<sup>1</sup>,

Shigehito Kiyokawa<sup>1</sup>, Koji Taneichi<sup>1</sup>, Takanori Azuma<sup>1</sup>, Toshiaki Miyamoto<sup>1</sup>, Michio Minami<sup>1</sup>, Tomomi Tsuru<sup>1</sup>, Munenori Mochizuki<sup>1</sup>, Yukio Sato<sup>1</sup>

<sup>1</sup>Japanese Clinician's Biologic Research Group, <sup>2</sup>Matsubara Mayflower Hospital

Conflict of interest: Yes

[Objectives] It is known that experience with BIO or lack thereof affects patient goals and other factors, but differences in treatment cost and time factors were unclear. A survey on these factors was done. [Methods] Written consent and background from 9437 RA patients from 51 facilities was obtained. A survey was taken regarding treatment cost, acceptance of BIO, examination times, wait times and other issues. Patients were divided into BIO (BG: 3363) and DMARDS groups (DG: 4535). [Results] Patients were 83% female, disease duration 10-20 years, age in the 50s most prevalent. In analysis of BIO cost, both groups showed an out-of-pocket cost of 5,000-10,000 yen per month, BG group slightly higher, with no difference by area. When offered use of BIO, 50% of patients in BG group responded 'will accept' or 'have accepted' vs. 50% of DG 'cannot answer'. For ideal examination time, the response of '5-15 minutes' was top in both groups, with no difference by area or type of medication, with a slight difference by area; in Chugoku 23% of respondents chose '10 minutes or less'. [Conclusion] There was no great difference in out-of-pocket costs or ideal examination time between the groups. There is a distinct possibility that there may be a difference in ideal waiting time by area.

### P3-048

#### Results of Multi-center Rheumatoid Arthritis (RA) Patient Survey (2) Results analyzed by area

Akira Sagawa<sup>1</sup>, Tsukasa Matsubara<sup>1,2</sup>, Hiroaki Matsuno<sup>1</sup>, Keiko Funahashi<sup>2</sup>, Yosuke Nishioka<sup>1</sup>, Tamami Yoshitama<sup>1</sup>, Norihiko Koido<sup>1</sup>, Masakazu Kondo<sup>1</sup>, Tomohiko Yoshida<sup>1</sup>, Yoshiki Shiohira<sup>1</sup>, Kenji Mannami<sup>1</sup>, Masaaki Yoshida<sup>1</sup>, Hideshi Yamazaki<sup>1</sup>, Katsuhiko Narushima<sup>1</sup>, Yasuhiko Hirabayashi<sup>1</sup>, Toyomitsu Tsuchida<sup>1</sup>, Masato Okada<sup>1</sup>, Takehiko Ayabe<sup>1</sup>, Atsuko Imai<sup>1</sup>, Yasuhiko Munakata<sup>1</sup>, Tatsuo Kotsuma<sup>1</sup>, Kazuyasu Ushio<sup>1</sup>, Shuji Abe<sup>1</sup>, Hideo Kagawa<sup>1</sup>, Takeshi Mitsuka<sup>1</sup>, Jiro Yamana<sup>1</sup>, Shinichi Ishioka<sup>1</sup>, Chiyuki Abe<sup>1</sup>

<sup>1</sup>Japanese Clinician's Biologics Research Group, <sup>2</sup>Matsubara Mayflower Hospital

Conflict of interest: Yes

[Objectives] BIO and DMARDS groups were compared; patient goals were high but other areas were unclear. A multi-center survey was done. [Methods] 9437 patients' consent and background was obtained from at 51 facilities. The survey asked desired information, expectations of medications, experiences of disappointment and reasons, anxiety when changing medication, BIO experience, treatment goals, degree of satisfaction, questions for health professionals etc by multiple choice and essay. Data was tabulated for 6 regions, Hokaido/Tohoku (1), Kanto (2), Chubu/Hokuriku (3) Kinki/Shikoku (4), Chubu (5) Kyushu (6). [Results] Rates of BIO and steroid usage differed. There were no large differences in 'expectations of medication', 'questions for health professionals' and 'disappointment with treatment' but 'reasons for disappointment', 'anxiety' and 'treatment goals' differed, seemingly linked with rate of BIO use; areas of higher BIO use had more 'worry over expense' and 'disappointment with efficacy' answers while 'prevention of joint destruction' was held as a goal. 'Satisfaction' was fairly uniform, at 70-75% overall. [Conclusion] The level of satisfaction was uniform, differing little by area. The rate of BIO use may have an effect on the reasons for patient anxiety and treatment goals.

### P3-049

#### The Effect of Pain Control on HAQ As Well As Disease Activity Control For Rheumatoid Arthritis Patient

Ichiro Yoshii

Yoshii Hospital from Medical Corporation Genyu

Conflict of interest: None

[Objectives] Patient's pain is important in treatment of rheumatoid arthritis (RA). We have investigated the effect of pain control on Health Assessment Questionnaire Disability Index (HAQ). [Methods] Relationship between HAQ and parameters that consist as core set of SDAI, SHS, patient's age, and pain VAS (PS) were evaluated statistically with linear regression analysis, while correlation between PS and the other parameters were also evaluated. These analyses were investigated at baseline and one year's period from 372 patients who have been followed up more than 3 years. [Results] Age and PS have demonstrated as the only factors that correlated significantly with HAQ throughout every year period. PS had also demonstrated significant close correlation with every core set of SDAI. This relationship had demonstrated both at baseline and every period. With multi variant linear regression analysis, PGA and TJC were the only factors that demonstrated significant close correlation with PS. These results demonstrated both at baseline and during followed up period. [Conclusion] These results suggested that pain is very important key to control both of ADL and disease activity.

### P3-050

#### Trajectories of EQ-5D in RA patients treated with biologics using the IORRA cohort

Daisuke Hoshi, Eisuke Inoue, Eiichi Tanaka, Rei Yamaguchi, Yoko Shimizu, Akiko Kobayashi, Naoki Sugimoto, Kumi Shidara, Eri Sato, Yohei Seto, Ayako Nakajima, Atsuo Taniguchi, Shigeki Momohara, Hisashi Yamanaka

Institute of Rheumatology Tokyo Women's Medical University

Conflict of interest: None

[Objectives] To identify subclasses with distinct trajectories of EQ-5D in RA patients who initiated biologics (BIO) and examine clinical features whose QOL improved after BIO use in daily practice. [Methods] The subjects were 813 RA patients who initiated BIO. We estimated the latent classes for the time trend of EQ-5D score for 3 years after initiation of BIO use. We estimated each patients' latent class based on posterior probability. We compared clinical characteristics of each latent class. [Results] Clustering the 813 patients based on the time trend of the EQ-5D score, they were classified into four classes; Class1 (N=164): patients with persistent low EQ-5D score (EQ-5D stayed under 0.6), Class2 (N=340): patients with persistent moderate EQ-5D score (EQ-5D stayed around 0.7), Class3 (N=91): patients whose EQ-5D score improved after BIO use (EQ-5D improved from 0.7 to 0.9), and Class4 (N=218): patients with persistent high EQ-5D score (EQ-5D stayed around 0.9). The patients in Class3 were younger ( $p<0.001$ ), shorter disease duration ( $p<0.001$ ), higher DAS28 ( $p<0.001$ ), lower J-HAQ ( $p=0.038$ ) and more frequent in non-steroid use ( $p=0.002$ ) than those in Class2. [Conclusion] We elucidated clinical features of RA patients whose QOL improved after BIO use in daily practice.

### P3-051

#### Initiation and escalation rate of methotrexate dose and the risk of side effects

Ayaka Yoshikawa, Shuzo Yoshida, Nao Tokai, Yoko Matsumura, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa

Department of Internal Medicine (I), Osaka Medical College, Osaka, Japan

Conflict of interest: None

[Objectives] We evaluated the rate of side effects associated with methotrexate (MTX), and whether the side effects were associated with the initiation and escalation rate of MTX dose. [Methods] In this study, 143 rheumatoid arthritis (RA) patients who started MTX therapy from January 2011 to July 2014 in our hospital were investigated. [Results] Of 143 RA patients, 116 were female. The mean age was  $59.8 \pm 14.0$  years, average body weight was  $58.8 \pm 37.7$  kg, mean disease duration was  $4.2 \pm 6.2$  years. Average MTX initiation dose was  $5.2 \pm 1.4$  mg / week and MTX dose after 12 weeks was  $8.2 \pm 2.5$  mg / week. The main side effects were hepatotoxicity in 29 cases (20.2%), gastrointestinal symptoms in 9 cases (6.3%), cytopenia in 6 cases (4.1%), and oral aphtha in 6 cases (4.1%). Eleven of 143 (7.7%) discontinued MTX treatment in the first 12 weeks. Hepatotoxicity was associated with MTX initiation dose

( $p<0.036$ ), but no association with MTX escalation rate after 4, 8, 12 weeks. [Conclusion] In clinical, initiation dose of MTX is associated with hepatotoxicity.

### P3-052

#### Correlation of sleep disturbance with disease activity, psychological state and health status in patients with rheumatoid arthritis

Chikako Yukioka<sup>1</sup>, Hideko Nakahara<sup>2</sup>, Mie Fusama<sup>2</sup>, Kumiko Yukioka<sup>1</sup>, Takanori Kuroiwa<sup>1</sup>, Miyako Inoue<sup>1</sup>, Tae Nakanishi<sup>1</sup>, Futoshi Yukioka<sup>4</sup>, Norikazu Murata<sup>1</sup>, Kayoko Higashi<sup>2</sup>, Taro Kuritani<sup>2</sup>, Keiji Maeda<sup>2</sup>, Yasushi Miura<sup>3</sup>, Hajime Sano<sup>4</sup>, Masao Yukioka<sup>1</sup>

<sup>1</sup>Yukioka Hospital, <sup>2</sup>NTT West Osaka Hospital, <sup>3</sup>Kobe University Graduate School of Health Sciences, <sup>4</sup>Hyogo College of Medicine

Conflict of interest: None

[Objectives] We evaluated which factor is correlated with sleep disturbance in patients with RA. [Methods] Sleep disturbance was assessed with PSQI. Correlation of PSQI was evaluated with SJC, TJC, PGA and EGA. Psychological factors were also examined utilizing CES-D, HADS-D, HADS-A and STAI. Health status was evaluated with SF-36. Data analyses were performed using Spearman correlation analysis. [Results] The patients with RA ( $n=112$ ) were recruited. Average of age: 54.8 years old, disease duration: 11.4 years, SJC: 2.7, TJC: 2.2, PGA: 23.2mm, EGA: 16.2mm. PSQI was not correlated with age, duration, SJC, TJC and EGA, while PSQI was weakly statistically correlated with PGA ( $r=0.2592$ ,  $p=0.0058$ ). As for psychological state, PSQI was significantly correlated with CES-D ( $r=0.5165$ ,  $p<0.0001$ ), HADS-A ( $r=0.4139$ ,  $p<0.0001$ ), HADS-D ( $r=0.4182$ ,  $p<0.0001$ ), STAI (State) ( $r=0.476$ ,  $p<0.0001$ ), while there was no statistically significant difference between PSQI and STAI (Trait). Although PCS of SF-36 was not correlated with PSQI, MCS was significantly correlated with PSQI ( $r=0.4186$ ,  $p<0.0001$ ). [Conclusion] Sleep disturbance was more correlated with psychological state rather than disease activity and physical state. Care for sleep disturbance may be important to improve psychological state.

### P3-053

#### Affective component of pain in rheumatoid arthritis

Tetsuji Hosozawa, Katsunori Ikari, Shigeki Momohara  
Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: None

[Objectives] The goal of Rheumatoid arthritis (RA) treatment is to achieve and maintain remission. However, some patients cannot achieve remission due to high patient global assessment (PGA). As PGA is greatly affected by pain, reducing subjectively noticed pain may improve PGA. Pain is mainly divided into sensory and affective components. The objective of this study is to investigate how affective elements of pain affect disease status in RA patients. [Methods] Our study included 5103 patients from the Institute of Rheumatology, Rheumatoid Arthritis (IOR-RA) cohort. We analyzed the relation between selection of words that represent affective pain from SF-MPQ and swollen joint count and tender joint count, PGA and CRP by using multiple logistic regression analysis. We also analyzed patients who lack only  $PGA\leq 1$ cm to fulfil Boolean remission. [Results] 862 patients selected words that represent affective pain. Affective pain were significantly related with PGA ( $p=10^{-164}$ ) and tender joint count ( $p=10^{-8}$ ) however, not with CRP ( $p=0.86$ ) and swollen joint count ( $p=0.44$ ). [Conclusion] Affective component of pain was significantly related with subjectively evaluated factors and not with objective factors.

### P3-054

#### Correlation of activities of daily living with psychological state in patients with rheumatoid arthritis

Kumiko Yukioka<sup>1</sup>, Hideko Nakahara<sup>2</sup>, Mie Fusama<sup>2</sup>, Chikako Yukioka<sup>1</sup>, Takanori Kuroiwa<sup>1</sup>, Sayuri Arimitsu<sup>1</sup>, Kumiko Kobayashi<sup>1</sup>, Jin Sawada<sup>1</sup>, Futoshi Yukioka<sup>3</sup>, Tae Nakanishi<sup>1</sup>, Miyako Inoue<sup>1</sup>, Keiji Maeda<sup>2</sup>, Norikazu Murata<sup>1</sup>, Suguru Osawa<sup>1</sup>, Masao Yukioka<sup>1</sup>

<sup>1</sup>Yukioka Hospital, <sup>2</sup>NTT West Osaka Hospital, <sup>3</sup>Hyogo College of Medicine

Conflict of interest: None

[Objectives] We evaluate correlation of activities of daily living (ADL) with psychological state in patients with rheumatoid arthritis (RA). [Methods] Assessment of psychological state was performed utilizing CES-D, a measure evaluating depression. ADL was evaluated utilizing MHAQ. The patients with RA were divided to depression group ( $CES-D\geq 16$ ) and non-depression group ( $CES-D<16$ ). MHAQ was compared between depression group and non-depression group. [Results] Twenty-one patients (3 males and 18 females) were enrolled. Average age: 54.4 years. Average disease duration: 16.6 years. Eight patients (38.1%) were in depression group. There is no significant difference in age, duration, Class, Stage and CDAI between depression group and non-depression group. No significant difference was also found in dosages of prednisolone and methotrexate. MHAQ of depression group was significantly lower compared with that of non-depression group ( $p=0.0123$ ). Moreover, HADS-A and HADS-D were also significantly higher in depression group compared with non-depression group ( $p=0.0231$ ,  $p=0.312$ , respectively). [Conclusion] Psychological state may be related with ADL in patients with RA, This results may suggest the importance of support for psychological state as well as treatment to improve ADL.

### P3-055

#### The study of Inflammatory pain and non-inflammatory pain (NIP) in rheumatoid arthritis

Takeshi Mochizuki<sup>1</sup>, Koichiro Yano<sup>2</sup>, Ryo Hiroshima<sup>1</sup>, Kosei Kawakami<sup>1</sup>, Hiromitsu Takaoka<sup>1</sup>, Naoko Koenuma<sup>1</sup>, Katsunori Ikari<sup>2</sup>, Shigeki Momohara<sup>2</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Kamagaya General Hospital, Chiba, Japan, <sup>2</sup>Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: Yes

[Objective] The study was conducted to examine inflammatory pain and non-inflammatory pain (NIP) in patients with rheumatoid arthritis (RA). [Method] The study examined 443 RA patients with disease duration of 10.6 years. Comparison was made between pain VAS  $\geq 30$  (Group P) and  $< 30$  (Group N). In addition, CRP and ESR were normal and pain VAS  $\geq 30$  (Group NIP) were also compared with pain VAS  $< 30$  (Group NINP). [Result] Comparing Group P (179 patients) with Group N (264 patients), there were significant differences in history of surgery, the use of steroids and analgesics, BMD of the hip and hand, ESR, MMP-3, DAS-CRP, DAS-ESR, SDAI, CDAI and HAQ. The multivariate analysis demonstrated a significant difference in CDAI only. Comparison between Group NIP (77 patients) and Group NINP (160 patients) showed significant differences in history of surgery, the use of steroids and analgesics, DAS-CRP, DAS-ESR, SDAI and CDAI. [Conclusion] Naturally, inflammation and history of surgery (progression of joint destruction) can cause severe pain. Meanwhile, approximately 20% of patients had NIP and severe pain can result in an increase in apparent disease activity and worsening HAQ. The analgesic treatment such as surgery and analgesics should be considered for patients with NIP.

### P3-056

#### Nodules in patients with rheumatoid arthritis and methotrexate treatment

Tadashi Nakamura<sup>1</sup>, Hirokazu Takaoka<sup>1</sup>, Yuko Watanabe<sup>1</sup>

<sup>1</sup>Kumamoto Shinto General Hospital, <sup>2</sup>Kumamoto Chuo Hospital, <sup>3</sup>Kumamoto University Hospital

Conflict of interest: None

Methotrexate (MTX) is a key drug in the treatment of RA and has various pharmacological modes of action. The actual mechanisms underlying the pathogenesis of the nodular disorders are still unclear. Great histopathological diversity exists in nodules in patients with RA because of rheumatoid disease activity and severity, MTX-induced adverse effects, and *in situ* reactivated Epstein-Barr virus (EBV), which occurs in MTX-associated lymphoproliferative disorders (LPDs). We describe the broad histopathological spectrum of nodules as related to the effects of MTX in patients with RA. Patients with RA may have various types of

nodules, including those of rheumatoid neutrophilic dermatitis, which is an infrequent cutaneous manifestation of RA with features of a heavy dermal infiltrate of neutrophils, a variable degree of leukocytoclasia, and no vasculitis. Other types include rheumatoid nodules, and MTX-induced accelerated rheumatoid nodulosis. Also, EBV-associated lymphomatoid granulomatosis during MTX therapy and MTX-associated LPD. Various histopathological findings of nodules in patients with RA having MTX treatment correlate closely with rheumatoid activity, immune function, and modes of MTX action.

### **P3-057**

#### **The 9 Cases of lymphoproliferative disorder (LPD) in Rheumatoid Arthritis**

Makoto Kurisuno, Yusuke Asano, Kazumasa Kitamoto, Yusuke Iwahori  
Department of Orthopaedic Surgery, Aichi Medical University, Nagakute, Aichi, Japan

Conflict of interest: None

[Objectives] The 9 (male; 1, female; 8) cases of LPD were developed between 2008 and 2014. An average age was 72.5 years old, an average RA disease duration was 23.5 years. The 6 cases were taken MTX (4-5mg/week), an average duration of MTX was 6.7years. [Methods] [Results] By the pathological diagnosis, 6 cases were DLBCL, 1 case was T cell lymphoma and 2 cases was unknown (that was natural regression by MTX cancellation). The 6 cases of DLBCL were treated with R-CHOP, but 1 case was infected MRSA and died. The case of T-cell lymphoma (76years old male and were taken Cyclophosphamide for 6 years) was infected CMV and died. [Conclusion] In our orthopedics department, 1 case in 2008, 1case in 2009, 1 case in 2010, 2 case in 2011, 2 case in 2013 and 2 cases in 2014 were developed. In this several years, We think the incidence of LPD was tend to increase. To reduce RA disease activity, We require a high dose MTX, combined other DMARDs and more bDMARDs for patients. Those over treatments may be induce LPD but not clear. It is necessary to gather a large number of cases to examine a risk of the LPD onset for the RA patient.

### **P3-058**

#### **Methotrexate-related lymphoproliferative disorder was misdiagnosed as a worsening of RA; a case report**

Kan Takase<sup>1</sup>, Sumio Ikenoue<sup>2</sup>

<sup>1</sup>Severe Trauma Center, Orthopaedic Surgery, Funabashi Medical Center, <sup>2</sup>Orthopaedic Surgery, Funabashi Medical Center

Conflict of interest: None

74 year old man had a right omalgia. 1 year after he saw our hospital with left hand index finger and right Achilles' tendon pain and RA was diagnosed (DAS28/CRP: 3.97). He received bucillamine but symptoms continued for 4 months, so 6mg/week of methotrexate started. Complete remission continued for 22 months. After then methotrexate gradually increased up to 12mg/week at 37 weeks after initial examination. He had sometimes a slight fever at 41 weeks after initial examination. At 43 weeks, white blood cell number increased and CRP became high. Because nothing but RA was recognized as a cause of inflammation, methotrexate increased up to 14mg/week. At 50 months, abnormal blood cells were recognized in peripheral blood so he examined by hematologist and methotrexate-related lymphoproliferative disorder was diagnosed. Immediately we stopped to prescribe methotrexate, after then abnormal blood cells disappeared and inflammation decreased. In case that the real RA activity (symptoms, X-P, MMP3 etc.) does not correlate to laboratory data, it is important to consider the possibility of MTX-LPD in MTX received RA patients.

### **P3-059**

#### **Investigation of patients with RA in the aspect of IMT(intima-media thickness of carotid artery) and Osteoporosis(lumbar vertebrae QCT=Quantitative Computed Tomography)**

Sadahiko Kameda<sup>1</sup>, Eiji Shirasawa<sup>2</sup>

<sup>1</sup>Kameda Internal Medicine Clinic, Mito, Japan, <sup>2</sup>Shirasawa Orthopedic Clinic, Morioka-city, Japan

Conflict of interest: None

Chronic rheumatoid arthritis (RA) mainly causes cartilage proliferation and bone destruction in joints organs, on the other hand, it causes other various lesions in addition to joints lesions. This time, we investigated IMT in carotid arteries and lumbar QCT in the patients with RA. Subject in this investigation is over 40 years old female patients with RA. IMT outcome figured out 0.75mm (40s aged), 0.77mm (50s aged), 0.78mm (60s aged), 1.0 (70s aged), and 1.5mm (80s aged). It indicated out higher titers in according to age transition. And that outcome existed between that of healthy persons and that of diabetes mellitus, in the aspect of age transition. In the relation between IMT and RA Stage, Stage 1 is 0.83mm, Stage2 is 1.06mm, Stage 3 1.2mm, Stage 4 is 1.1mm. IMT titers in RA patients are accelerated in accordance to Stage. The relation index between IMT and lumbar vertebrae QCT is -0.35. The titer of QCT, at that of 40s aged cases with RA and 50s aged cases are lower titer than non-RA cases. However, that of 60s aged RA and 70s aged RA are higher titers than non-RA cases. These higher titers can be considered as the effect of early management for osteoporosis preventing in RA cases in comparison with non-RA case.

### **P3-060**

#### **Vascular endothelial dysfunctions are detectable by using instant measurement in RA patients**

Ryosuke Hanaoka<sup>1</sup>, Junya Nagasawa<sup>1</sup>, Ayae Tanaka<sup>2</sup>

<sup>1</sup>Department of Rheumatology, Kamitsuga General Hospital, Tochigi, Japan, <sup>2</sup>Department of Pulmonary Medicine and Clinical Immunology, Dokkyo Medical University, Tochigi, Japan

Conflict of interest: None

[Objectives] To determine whether vascular endothelial dysfunctions are detectable by instant measurement in patients with rheumatoid arthritis. And if so, we investigated the relationship between vascular endothelial dysfunction and disease activity in RA patients. [Methods] We measured brachial-ankle pulse wave velocity; baPWV of 70 patients with RA and 134 non-RA individuals at baseline, one year and two years later. In RA patients, we measured intima-media thickness; IMT at same period. [Results] At baseline, baPWV levels were higher in RA patients compared with non-RA individuals (1578.8±366.0cm/s vs. 1510.0±281.1cm/s, P=0.000). After 2 years, RA patients had significantly greater increase of baPWV levels than those of non-RA (4.70±18.3% vs. -4.90±9.16 %). After the adjustment for confounding factors by multiple linear regression analysis, RA was identified as independent risk factor of deterioration of baPWV (P = 0.000). Among the patients with RA, the patients who used biologics for more than one year had significantly greater decline of IMT compared with other patients (-5.53 ± 27.06 % vs. 4.02 ± 20.40 %). [Conclusion] Endothelial dysfunctions are detectable by instant measurement in RA patients. Moreover, vascular endothelial dysfunction is related to disease activity in RA patients.

### **P3-061**

#### **A case that cervicodynia extinguished by the administration of a tumor necrosis factor alpha inhibitor**

Shohei Anno<sup>1,2</sup>, Koji Mandai<sup>3</sup>, Tatsuya Koike<sup>1,2</sup>

<sup>1</sup>Shirahama Hamayu Hospital, Wakayama, Japan, <sup>2</sup>Serch Institute for Bone and Arthritis Disease, Wakayama, Japan, <sup>3</sup>Shiraniwa Hospital, Nara, Japan

Conflict of interest: None

A case was 35-year-old woman. She had suffered from cervical pain for several years without clear episode. At the first visit of August in 2013, she had tenderness and swollen at PIP joint of right middle finger as well as cervical pain. The titer of RF and anti-CCP antibody was 47.5 u/mL and 13.5 mg/dl, but MMP-3, CRP and ESR showed normal range. There was an atlantoaxial subluxation by rentogenogram and a synovitis region around the dens by MRI and ultrasonography revealed the existence of power Doppler 1 signal on bilateral wrist. We diagnosed her cervical pain was derived from synovitis due to rheumatoid arthritis (RA). We started to treat with MTX (8 mg/week) and sulfasalazine (1000 mg/day). The symptoms except cervical pain disappeared and DAS28-CRP



decreased to 3.06 from 4.45 at the starting of treatment. And so we started biological treatment by Infliximab (3 mg/kg) in November, 2013. Her cervical pain decreased step by step and disappeared in May, 2014. The Synovitis region became reduced in size by MRI. Some researchers reported the synovitis of the cervical region with RA patients, but there was no literature about the treatment with biologics. For unidentified cervicodynia, a differential diagnosis of the rheumatoid arthritis should be carried out for a case.

### **P3-062**

#### **A case of large pulmonary rheumatoid nodules complicated systemic vasculitic lesions**

Kazuhiro Hatta, Shuko Hashimoto, Teruhisa Azuma, Hiroyasu Ishimaru  
Department of General Internal Medicine, Tenri Hospital, Tenri, Japan

Conflict of interest: None

We reported the rare RA case complicated with large pulmonary nodules and systemic vasculitic lesions. A 63 year-old female patient has been our clinic for the further exam of pulmonary lesion. She was pointed out asymptomatic pulmonary nodules on Xp. Her skin eruption biopsy showed vasculitis-like change, she was diagnosed to be malignant RA with pulmonary nodules. She seemed to be treated medically, but one day newly skin change appeared on her legs, and she lost her left vision because of newly developed vasculitis. Her left leg and right fingers were amputated. After operation, rather stable condition continued and PSL was successfully tapered. Then again she became feet severe headache, and CT showed sinusitis like lesion which disclosed to be granulomatous lesion suggestive of vasculitis. PSL doses became increased now, but nowadays Biomarker of fungal infection (Aspergillus Ag,  $\beta$ D-glucan) became to be positive. Now we should pay much attention to newly fungal infections in addition to. RA disease activities.

### **P3-063**

#### **Rheumatoid meningitis occurring during treatment with golimumab and tacrolimus: a case report**

Mizuho Muramatsu, Takayoshi Soga

Division of Rheumatology, Japanese Red Cross Shizuoka Hospital, Shizuoka, Japan

Conflict of interest: None

A 81-year-old woman with a 12-year history of rheumatoid arthritis was treated with golimumab and tacrolimus for the last one year and three months. She maintained low disease activity. On 23 June 2014, she was admitted with a 1-week history of intermittent dysarthria and right hemiparesis. She was diagnosed with transient ischemic attack and given cilostazol. She improved gradually. On 25 August, she developed lethargy and right hemiparesis. Brain magnetic resonance imaging (MRI) showed high intensity lesions in the subarachnoid space over the left cerebral hemisphere on the FLAIR image and The diffusion-weighted image (DWI). Cerebrospinal fluid analysis revealed raised cells and proteins. A brain and meningeal biopsy showed inflamed meninges with necrotizing in a part. Consequently, she was diagnosed with rheumatoid meningitis based on these findings. After treatment with 1000mg intravenous methylprednisolone for 3 days, followed by 35mg/day (1mg/kg/day) oral prednisolone, she showed improvements in disturbance of consciousness, right hemiparesis, cerebrospinal fluid findings and abnormal high intensity on MRI. Rheumatoid meningitis is an extremely rare neurological manifestation. We report here on a case with reference to the up-to-date literature.

### **P3-064**

#### **A case of rheumatoid arthritis diagnosed with pulmonary amyloidosis by TBLB**

Michiko Morishita<sup>1</sup>, Tomoko Kawabata<sup>1</sup>, Keiji Ohashi<sup>1</sup>, Yoshia Miyawaki<sup>1</sup>, Eri Katsuyama<sup>1</sup>, Takayuki Katsuyama<sup>1</sup>, Haruki Watanabe<sup>1</sup>, Mariko Narazaki<sup>1</sup>, Noriko Toyota Tatebe<sup>1</sup>, Koichi Sugiyama<sup>1</sup>, Katsue Sunahori Watanabe<sup>1</sup>, Hiroshi Wakabayashi<sup>1</sup>, Ken-ei Sada<sup>1</sup>, Jun Wada<sup>1</sup>, Hirofumi Makino<sup>2</sup>

<sup>1</sup>Department of Medicine and Clinical Science, Okayama University

Graduate School of Medicine Dentistry and Pharmaceutical Sciences, Okayama, Japan, <sup>2</sup>Okayama University Hospital, Okayama, Japan

Conflict of interest: None

A 57-year-old male with a history of exposure to smoke and asbestos was diagnosed with rheumatoid arthritis (RA) in 2007, although he left the disease untreated. He developed a chronic cough in January 2014 that subsequently worsened and began to feel pain in multiple joints in July. He was seen at another clinic, where he was found to have multiple pulmonary nodules with left pleural thickening and effusion on CT. In late August, he was admitted to our hospital with a fever and deteriorating cough and pleural effusion. Laboratory data: WBC= 12210/ $\mu$ l, CRP= 10.9 mg/dl, ESR= 121 mm/h, ANA (-), RF= 492 U/ml, anti-CCP antibody= 90.2 U/ml, SAA= 164  $\mu$ g/ml, KL-6= 120 U/ml, CYFRA= 3.1 ng/ml, SCC= 0.8 ng/ml, QFT (-) and blood culture (-). PET-CT showed a high FDG uptake in the area of left pleural thickening and a poor uptake in the pulmonary nodules. Although he was treated for severe periodontitis after admission, the improvement in the inflammatory response was slight. Sputum and pleural effusion analyses were inconclusive; however, amyloid was detected on TBLB, while a pleural biopsy showed no malignancy. Therefore, PSL and MTX were administered for RA. This case is considered to be valuable in that a diagnosis of reactive pulmonary amyloidosis was detected in a RA patient on TBLB.

### **P3-065**

#### **Efficacy of additional tacrolimus additional administration on rheumatoid arthritis patients intolerant irresponsive to biologics**

Kenji Takahashi<sup>1</sup>, Akiko Sato<sup>1</sup>, Sanshiro Hashimoto<sup>2</sup>, Toshikazu Kamada<sup>3</sup>, Masahito Koiwa<sup>4</sup>, Shinro Takai<sup>1</sup>, Hiroshi Nakamura<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Nippon Medical School, Graduate School of Medicine, Tokyo, Japan, <sup>2</sup>Minami-Shinjuku Orthopaedic Rehabilitation Clinic, <sup>3</sup>Hara Orthopaedic Hospital, <sup>4</sup>Department of Orthopaedic Surgery, Shuwa General Hospital

Conflict of interest: None

[Objectives] We consider the additional administration of low dosages of tacrolimus (TAC) in cases of inadequate effects of RA cases treated with biologics. [Methods] We investigated 14 cases (3 male and 11 female), with an average age of 63.4 $\pm$ 10.9 years. The biologics used were 6 cases of anti-TNF, 4 cases of tocilizumab (TOC) and 4 cases of abatacept (ABT). The added TAC was co-administered with an average of 1.0 mg. The effects of TAC co-administration were determined based on the EULAR criteria. [Results] With the addition of TAC, a good or moderate response was observed in 1 case (17%) of anti-TNF biologics use, 2 cases (50%) of TOC use, and 4 cases (100%) of ABT use. There were no severe adverse events. [Conclusion] Cases of inadequate effects of biologics is often considered by increasing the MTX dosage, increasing or changing the biologics. However, there are many cases in which appropriate management is difficult due to the underlying medical condition. In the present study, addition of a small amount of TAC was effective in about half the cases. In particular, responsiveness was high in cases with ABT, in which T-cell activity inhibition is the action mechanism. The number of adverse events was small, and this may be a useful option in cases of inadequate effects of ABT.

### **P3-066**

#### **Efficacy of tramadol hydrochloride/acetaminophen combination tablets in elderly patients with rheumatoid arthritis**

Naofumi Yamauchi<sup>1</sup>, Koji Ihara<sup>2</sup>, Takuji Nishisato<sup>2</sup>

<sup>1</sup>Department of Rheumatology, Sapporo Kiyota Hospital, <sup>2</sup>Department of Internal Medicine, Sapporo Kiyota Hospital, <sup>3</sup>Department of Rehabilitation, Sapporo Kiyota Hospital

Conflict of interest: None

[Objective] Elderly patients with RA are less likely to receive effective therapies (biologics, DMARDs and NSAIDs) due to increased risk of infections and complications than younger patients with RA. Therefore, in some elderly RA patients, ADL are deteriorated caused by chronic pain. We investigated the efficacy of tramadol/acetaminophen combi-

nation tablets (TRAM/APAP) in elderly RA patients with uncontrolled chronic pain. [Methods] We examined 51 RA patients receiving TRAM/APAP, 29 patients were 65 years or older (elderly group, 78.7±7.3 years) and 22 were younger than 65 years (younger group, 54.7±10.8 years). The clinical response was assessed by VAS (mm) and HAQ-DI. [Results] The mean VAS score decreased from 67.0 before administration to 34.2 at week 4 and 33.8 at week 8 after administration (elderly group), from 64.8 to 41.3 and 35.3 (younger group), respectively. The mean HAQ-DI score improved from 1.75 to 1.18 at week 4-8 (elderly group), from 0.88 to 0.55 (younger group), respectively. The incidence of adverse events was not different between two groups. [Conclusion] TRAM/APAP was highly effective for chronic pain and improved ADL of elderly RA patients as well as younger RA patients. Use of TRAM/APAP is a valuable treatment option for elderly RA patients with chronic pain.

### P3-067

#### The evaluation of the efficacy and safety of tramadol hydrochloride/acetaminophen in 80 cases

Aihiro Yamamoto, Aiko Tominaga, Risa Sagawa, Takashi Kida, Amane Nakabayashi, Kazuki Fujioka, Yuji Kukida, Wataru Fujii, Ken Murakami, Takahiro Seno, Masataka Kohno, Yutaka Kawahito  
Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: None

[Objective] To evaluate the efficacy and safety of tramadol hydrochloride/acetaminophen in the control of pain. [Methods] We reviewed the 80 cases that were prescribed tramadol hydrochloride/acetaminophen (T/A) until December, 2013. [Results] The mean age was 60.2 years old and the cases included 67 women. Sixty cases were Rheumatoid arthritis (RA), and biological agents were administered to 16 cases among them when T/A was started. Forty-four cases showed effectiveness, and 34 cases continued the administration for more than six months. Five of eight cases that PSL were given more than 10 mg/day were able to reduce PSL dosage. Serum CRP level did not show the statistical significant difference between continuation group and discontinuation group for 24 weeks, but the mean serum creatinine level was significantly higher in the discontinuation group (0.71 mg/ml) than that of the continuation group (0.57 mg/ml). The most common reason of T/A discontinuation was improvement of pain in 12 cases and then vomiting in 9 cases. [Conclusion] For RA patients of advanced age or with renal dysfunction, the administration of T/A before DMRADs and biological agents exhibit the effectiveness may be useful for avoiding NSAIDs or corticosteroids use for a long period.

### P3-068

#### Hepatitis B virus reactivation following salazosulfapyridine monotherapy in a patient with rheumatoid arthritis

Kengo Akashi<sup>1</sup>, Jun Saegusa<sup>1</sup>, Yuji Nakamachi<sup>2</sup>, Takashi Nakazawa<sup>3</sup>, Shunichi Kumagai<sup>4</sup>, Akio Morinobu<sup>1</sup>

<sup>1</sup>Department of Rheumatology and Clinical Immunology, Kobe University Graduate School of Medicine, Kobe, Japan, <sup>2</sup>Department of Clinical Laboratory, Kobe University Hospital, Kobe, Japan, <sup>3</sup>Department of Rheumatology, Saiseikai Nakatsu Hospital, Osaka, Japan, <sup>4</sup>The Center for Rheumatic Diseases, Shinko Hospital, Kobe, Japan

Conflict of interest: None

SASP has received little attention when discussing HBV management in RA patients because there have been no reports of de novo hepatitis induced by SASP. This is a rare case of de novo hepatitis that developed in a male RA patient during SASP monotherapy. RA was diagnosed when he was 72 years old. Serological findings suggested a prior HBV infection; negative for HBsAg and HBV-DNA, and positive for HBsAb and HBcAb. He began treatment with SASP, and the RA promptly went into clinical remission. He remained on SASP monotherapy thereafter. When he was 74 years old, his blood tests showed slightly elevated liver function. Serum tests were positive for HBsAg and HBV-DNA. The diagnosis was de novo hepatitis due to SASP. He continued SASP and began entecavir, and the liver-function-test values and serum HBV viral load gradually returned to a normal range. ATP-binding cassette protein

G2 (ABCG2) and N-acetyltransferase 2 (NAT2) are associated with absorption and metabolism of SASP. *ABCG2* and *NAT2* gene exhibit hereditarily determined polymorphism. It is reported that these polymorphisms are related with efficacy and toxicity of SASP. We examined our patient's *NAT2* and *ABCG2* genotypes; he was found to have *NAT2\*6A/\*6A* and *ABCG2-A/A*, correlated with high efficacy and high toxicity.

### P3-069

#### Two cases of rheumatoid arthritis patient successfully treated by biologic therapy with tacrolimus, but induced to interstitial pneumonia with methotrexate

Hiroki Wakabayashi<sup>1</sup>, Masahiro Hasegawa<sup>1</sup>, Yosuke Nishioka<sup>2</sup>, Kusuki Nishioka<sup>3</sup>, Akihiro Sudo<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, <sup>2</sup>Nishioka memorial Central Clinic, <sup>3</sup>Institute of Medical Science, Tokyo Medical University

Conflict of interest: None

[Objectives] We reported that two cases of rheumatoid arthritis (RA) patient successfully treated by biologic therapy with tacrolimus, but induced to interstitial pneumonia with methotrexate (MTX). [Case reports] In case 1, a 67-year-old man with RA treated with abatacept due to multiple biologics failure. He successfully treated with abatacept plus MTX. However, he was induced to interstitial pneumonia, so he stopped MTX. He failed to RA disease activity with abatacept monotherapy. So he successfully treated with abatacept plus tacrolimus. In case 2, a 68-year-old man with RA treated with certolizumab pegol plus MTX. But he was elevated interstitial pneumonia marker. So he changed to treatment with tacrolimus and successfully treated with certolizumab pegol plus tacrolimus. [Conclusion] We suggest that interstitial pneumonia is required to care in RA patients treated with biologic agents plus MTX.

### P3-070

#### Adverse drug reaction of Salazosulfapyridine mimicing polymyalgia rheumatica complicated with giant cell arteritis

Shunsuke Mori, Tomoya Miyamura, Masataka Nakamura, Makiko Higuchi, Shoko Kodama, Yu Kaku, Soichiro Takahama, Rumi Minami, Masahiro Yamamoto, Eiichi Suematsu

National Hospital Organization Kyushu Medical Center

Conflict of interest: None

A 64-year-old woman, who had been diagnosed as pustulotic arthro-osteopathy in September 2003, was treated with Salazosulfapyridine (SASP) over ten years. Because she suffered from fever, bilateral shoulder arthralgia, jaw claudication and a temporal pain in May 2014, she was admitted to our hospital on June 3<sup>rd</sup>. Hematological testing showed a severe inflammation and a mild liver dysfunction without any evidence of infection. There were not any findings of synovitis and temporal arteritis on ultrasound examination and PET-CT scanning, although we suspected polymyalgia rheumatica (PMR) complicated with giant cell arteritis (GCR) on the basis of clinical symptoms. We considered the possibility that pleiotropic manifestations were caused by SASP, so that this drug was discontinued on June 21<sup>th</sup>. As her symptoms and serological abnormalities were completely improved 12 weeks later, and drug-induced lymphocyte stimulation test revealed a high stimulation index for SASP, we concluded adverse drug reaction (ADR) of SASP. ADR of SASP has been well described such as skin lesions and gastrointestinal symptoms, but this case alerted us that SASP might have a potential to induce a bizarre ADR.

### P3-071

#### Pure red cell aplasia (PRCA) induced by salazosulfapyridine (SASP) in an elderly woman with rheumatoid arthritis (RA)

Emi Tsujino, Teruhisa Azuma, Shuko Hashimoto, Hiroyasu Ishimaru, Kazuhiro Hatta

Tenri Hospital, Nara, Japan

Conflict of interest: None

[present illness] A 78-year-old Japanese woman was started on SASP for RA, concurrent with scleroderma and interstitial pneumonia, 2 months before admission. About 4 weeks later, she developed dyspnea on exertion and general malaise, with progressive anemia, but no intestinal bleeding was detected on endoscopy. On regular visit, she was admitted because of severe anemia. [physical examination] appearance: chronically ill and pale, conjunctivae: anemic, heart: Levine III/VI apical holosystolic murmur, lungs: fine crackles at bilateral lung fields, rectal exam: no tarry stool [laboratory studies] Hb 6.3g/dl (before admission, Hb 11.4 g/dl), MCV 91fl, serum iron 193µg/dl, TIBC 209µg/dl, ferritin 424ng/ml, Ret 0.3%, haptoglobin 59.0mg/dl, Vit B12 754pg/ml, folic acid 6.2ng/ml [clinical course] Bone-marrow smear revealed PRCA. Anti-human parvovirus B19 antibody was negative. Within 16days of SASP withdrawal, reticulocytes began to elevate, followed by recovery of Hb level. We diagnosed drug-induced PRCA, probably due to SASP. [clinical importance] Macrocytic or hemolytic anemia by SASP are reported occasionally, but PRCA caused by SASP are rare. This case indicates that it is possible for patients with normocytic and non-hemolytic anemia treated with SASP to develop drug-induced PRCA.

### P3-072

#### 3 cases of Methotrexate related Lymphoproliferative disorders in rheumatoid arthritis

Rui Kawato<sup>1</sup>, Koji Takasugi<sup>1</sup>, Yukari Murai<sup>2</sup>, Shun Minatoguchi<sup>2</sup>, Mitsuru Watanabe<sup>1</sup>, Toshikazu Ozeki<sup>2</sup>, Atsushi Nomura<sup>1</sup>, Tatsuhito Tomino<sup>1</sup>, Hideaki Shimizu<sup>2</sup>, Yoshiro Fujita<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Chubu Rosai Hospital, Nagoya, Japan,

<sup>2</sup>Department of Nephrology, Chubu Rosai Hospital, Nagoya, Japan

Conflict of interest: None

[Objectives] We report 3 cases of lymphoproliferative disorders (LPD) developed during Methotrexate (MTX) therapy for rheumatoid arthritis (RA). Case 1: a 64-years-old woman, diagnosed with RA 16 years ago. She takes MTX 6 mg orally a week. She is evaluated for fever and cough. There is no pain, swelling in her joints. CT shows bilateral Adrenal tumor and lymphadenopathy. Case 2: a 75-year-old woman, diagnosed with RA 1 year ago. She takes salazosulfapyridine 1g and Bucillamine 200 mg a day, MTX 4 mg a week. She noticed bilateral inguinal stiffness 2 months ago. It became bigger gradually. CT shows axilla, abdominal, inguinal lymphadenopathy. Both cases are diagnosed with LPD by biopsy. Lymphadenopathy became smaller after MTX discontinuation. Case 3: a 77-year-old man recognizes bilateral adrenal tumor in CT during MTX, infliximab therapy for RA and is diagnosed with malignant lymphoma by biopsy. After infliximab and MTX discontinuation, tumor reduced, but, because of high disease activity, we used rituximab 500 mg (day0,14) every 16 weeks, and DAS28 remitted. [Conclusions] RA with high disease activity is a high risk of lymphoma. MTX is known to cause LPD. We should take care of the development and relapse of LPD in the patients with high disease activity and using MTX.

### P3-073

#### A case of nephrosis syndrome developing during rheumatoid arthritis (RA) treatment

Michio Fujiwara, Yasuhiko Kita

Department of Rheumatology, Yokohama Rosai Hospital

Conflict of interest: None

A 67-year-old started prednisolone (PSL) treatment in 2007 in a clinic for RA. Thereafter, she visited us and achieved a complete remission after co-administration of tacrolimus (TAC). In December 2011, urinary protein was positive; the level showed an increase to 1.46 g/g Cre in March 2012. TAC was discontinued because of suspected drug-induced renal disorder, and switched to mizoribine (MZR), after which the protein level was further increased. In December 2012, MZR was discontinued and switched to PSL alone. However, the level was further increased, leading to hypoalbuminemia and nephrotic syndrome. Renal biopsy, performed in April 2013, raised suspicion of secondary membranous nephropathy. Lower gastrointestinal endoscopy revealed sigmoid colon cancer. There has been no postoperative recurrence and urinalysis findings have tended to show improvement since sigmoid colon resection in

June 2013. In this case, we considered drug-induced renal disorder as a major renal complication associated with RA. Finally, renal biopsy led to a diagnosis of secondary membranous nephropathy. This case highlights that urinary monitoring for renal disorder is important during RA treatment and renal biopsy for abnormal findings is useful for determining the causes.

### P3-074

#### Successful treatment with Igratimod in a case of Rheumatoid arthritis (RA) complicated tuberculosis

Takao Yamanaka

National Hospital Organization Minami-Okayama Medical Center Division of Rheumatology, Okayama, Japan

Conflict of interest: None

If the anti-TB therapy has been done, We often have suffered from what treatment against RA is better for RA patient. We report a case of successful treatment with Igratimod for RA complicated tuberculosis. [Cases] 76 year-Old woman This lady has suffered from RA since 2006 (Stage II Class3) and rheumatoid arthritis-associated interstitial lung disease (RA-ILD). Past History: Breast cancer on 2010 History of Present Illness; This lady consulted a nearby doctor (Orthopedic Suregen). Buc, SASP was is ineffective. She was introduced MTX to control RA. Indeed the drug response to RA had been good, but She was referred to internal medicine owing to MTX-induced pneumonitis in the same hospital. The rapid and complete improvement of the disease with steroid pulse therapy and tapering steroid. Because of suffered from Pulmonary tuberculosis, she was referred to our hospital on July. Sputum Gafky 8. Anti-TB drug therapy HES and LVFX against tuberculosis was done. Owing to tuberculosis of lymph nodes, the Anti-TB drug therapy HR has continued. In spite of PSL therapy (15mg per day) for RA and RA-ILD, she felt strong pain and joint swelling. We introduced iglacimod for RA arthritis. The activity of RA hasn't recurred, even to PSL tapering

### P3-075

#### Contributing factors related to infectious disease events during the treatment with biologic DMARDS in rheumatic diseases

Shinji Motojima, Tamao Nakashita, Akira Jibatake, Kotaro Matsumoto, Akira Yoshida, Yuto Hamada

Kameda Medical Center, Rheumatology and Allergy, Kamogawa, Japan

Conflict of interest: None

There are 252 patients with rheumatic diseases to date who had treatment with biologic DMARDS (bDMARDS) and the total number of bDMARDS was 431 because some of the patients changed bDMARDS during the course. The number of infectious disease events (IDEs) during the treatment was 283 and DIEs which needed hospitalization (severe IDEs, SIDEs) was 41. We tried to extract contributing factors related to IDEs. We checked items in clinical charts such as age, gender, stage, class, kind of bDMARDS, duration of administration, complications, doses of PSL and MTX, and diagnosis of IDEs, and discriminant analysis was done. There were no differences in the incidence of IDEs among 7 bDMARDS, but TCZ showed significantly higher incidence in bacterial skin infections. Significant discriminant coefficients related to the development of IDEs were the dose of PSL and the duration of administration. In regard to SIDEs, only the dose of PSL was significant, with age close to be significant. When patients were divided into 3 groups, namely SIDEs, IDEs and no-infection-group, significant discriminant coefficients were the dose of PSL, the duration of administration, and age. In conclusions, the common discriminant factor was the dose of PSL despite of different types of analysis.

### P3-076

#### Safety of Golimumab in Patients with Rheumatoid Arthritis in Japan in Light of Results of Drug Use-Results Survey

Atsushi Kawakami<sup>1</sup>, Masayoshi Kanbori<sup>2</sup>, Yoshimasa Ogawa<sup>2</sup>, Tsutomu Yajima<sup>3</sup>, Tomoyo Kawagishi<sup>2</sup>

<sup>1</sup>Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences,

<sup>2</sup>Japan Safety & Surveillance Division, Research & Development Division, Janssen Pharmaceutical K.K., <sup>3</sup>Biostatistics Department, Research & Development Division, Janssen Pharmaceutical K.K.

Conflict of interest: Yes

[Objectives] The drug use-results survey was conducted to evaluate the safety profile of golimumab in patients with RA in Japan. [Methods] The drug use-results survey for golimumab was conducted to evaluate the safety profile under the actual clinical conditions of usage (24 weeks). The survey was conducted as an all-cases survey at contract facilities using a central registry system (patients who started receiving golimumab prior to conclusion of the contract were included). [Results] The incidence of adverse drug reactions (ADR) was 15.03% in 5137 subjects of the safety analysis population; in System Organ Class (SOC), "Infections and infestations" was most frequently noted at 6.46%. The incidence of serious ADR was 4.96%, and the most frequent serious ADR was "pneumonia" of 0.66%. A multivariate logistic regression analysis identified functional impairment criteria of RA (Class III and Class IV), past medical history and/or complication of diseases of respiratory system, and past medical history and/or complication of renal impairment as factors that can increase the risk for serious infections. [Conclusion] The safety profile of golimumab observed in the drug use-results survey was similar to that observed in clinical trials and appeared to be similar with other TNF inhibitors.

### P3-077

#### **A Case Report: A Patient who suffered from Late-onset Infection on Both Sides of the Artificial Knee Joints during Biological Treatment**

Koichi Kitamura, Satoshi Nuka, Osamu Sato  
Orthopedic Department, Goryokaku Hospital

Conflict of interest: None

[Objectives] Late-onset infection that occurs more than one year after TKA is rarely experienced in immune suppressed patient. Artificial joint for the destroyed joints in RA is essential. This time, we report that a patient who suffered from late-onset infection on both sides of the artificial knee joints during biological treatment. [Case] 82-year-old woman, Steinbrocker S4, C2, disease duration was 58 years. Both TKAs were taken 7 years ago. Etanercept treatment was started 18-mo ago. She had severe pain in left knee and visited to our hospital. Joint fluid was purulent, so that immediate irrigation and administration of antibiotics could subside inflammation. 2-mo later, Etanercept was resumed and 4weeks later, infection had recurred. Irrigation and antibiotics administration had no effect, then, implants of her knee were needed removal. 3-mo later, reTKA was done. There was no sign of infection on her knee more than 1 year. RA got worse gradually, that needed golimumab treatment. After 4-mo of start of golimumab, swelling of right knee was occurred. The fluid was purulent, so right knee was needed irrigation and antibiotics. This time, the joint was preserved. [Conclusion] Biological agents should not be used for patients who had had late-onset periprosthetic infection.

### P3-078

#### **The clinical study of timing of resumption period and continuing status of biological agents after bacterial infection in the limbs of patient with rheumatoid arthritis**

Hajime Yamanaka<sup>1</sup>, Hiroshi Tamai<sup>1</sup>, Tatsuya Kobayashi<sup>1</sup>, Makoto Sueishi<sup>2</sup>, Takao Sugiyama<sup>2</sup>

<sup>1</sup>Department of Orthopaedic Surgery, National Hospital. Organization Shimoshizu Hospital, <sup>2</sup>Department of Rheumatology, National Hospital. Organization Shimoshizu Hospital

Conflict of interest: None

[Objective] To investigate the timing of resumption time and continuing status of biological agents after bacterial infection in the limbs of patient with rheumatoid arthritis. [Materials and Methods] From 2004, 12 patients, 14 legs (one man one leg, 11 female 13 legs) were treated with bacterial infections in the limbs of RA patients during using biological agents. We investigated retrospectively that whether to resume or not

the biological agents after the infection had healed. [Results] Infected patients were lower thigh phlegmonous inflammation 5 leg, deep infection after TKA 3 leg, superficial infection after TKA subcutaneous infection 1 leg, deep infection after TEA 1 upper limb, purulent tenosynovitis 1 finger, septic knee 1 leg, and thigh abscess 1 leg. Agents that have been used were ETN 7 limbs, IFX 2 limbs, TCZ 2 limbs, ADA 1 limb, and ABT1 leg at the time of infection happened. After infection healed, 2 patients, 2 limbs were quitted the biological agent. 6 patients, 8 limbs were resumption the use of same agents before infection, 4 patients 4 limbs were use of deferent agents before infection. [Discussion] If the condition of infection has improved, it should be restart the use of biological agent as soon as possible to prevent the RA condition worse.

### P3-079

#### **A case of rheumatoid arthritis complicated by IgA nephropathy exacerbation following etanercept therapy**

Osamu Asai, Kimihiko Nakatani  
Department of Nephrology, Kyoto Yamashiro General Medical Center, Kizugawa, Japan

Conflict of interest: None

A 43-year-old was diagnosed with rheumatoid arthritis (RA) at 31 years old and has been treated with salazosulfapyridine because of hepatitis B (HB) virus carrier. With RA activity been increasing, etanercept (ETN) was administered in combination with entecavir in 200X-1. At the starting of ETN, his urinalysis revealed proteinuria (-) and occult blood (3+). Several months later, his proteinuria level was elevated (0.56g/gCr), then, renal biopsy was performed. Renal biopsy showed minor glomerular abnormalities with mesangial IgA deposition. He was diagnosed with IgAN and treated with ARB. However, second renal biopsy was performed in 200X because of increased proteinuria level (2.5g/gCr) and worsening renal function (Scr 1.96mg/dl). Second renal biopsy was performed and revealed the progression of IgAN. Moreover, HB surface-antigen positive cells were not detected by immunohistochemical staining of renal biopsy. He was diagnosed as ETN-associated IgAN exacerbation and administered oral prednisolone (30mg/day) following discontinuation of ETN, resulting the reduction of proteinuria and improvement of renal dysfunction. This is the first case of RA complicated with ETN-associated IgAN exacerbation.

### P3-080

#### **A case of infectious endocarditis (IE) complicated by hepatic cirrhosis and nephrotic syndrome leading to serious hypoalbuminemia during adalimumab and methotrexate therapy for rheumatoid arthritis (RA)**

Soichi Yamada, Jo Nishino, Konomi Ashihara, Akiko Yoshida, Daisuke Hirano, Satoru Onoda, Kenichi Kato, Shusaku Fukaya, Shunji Yoshida  
Section of Rheumatology and Infectious Disease, Department of Internal Medicine, Fujita Health University School of Medicine, Aichi, Japan

Conflict of interest: None

History of present illness: At 55 years old (year X), she developed RA. At X+4 year, adalimumab and methotrexate (MTX; 14 mg/w) therapy was started and the arthralgia resolved. At X+8 year, she experienced pyrexia and low back pain and was immediately admitted. Course: Methicillin-sensitive *Staphylococcus aureus*(MSSA) was detected in blood culture and vegetations were observed on transesophageal echocardiography leading to a diagnosis of IE. Lumbar magnetic resonance imaging with contrast revealed a deep abscess and the presence of MSSA was confirmed in the abscess fluid. During the course of treatment, nephrotic syndrome developed. Findings of hepatic cirrhosis and ascites were observed on abdominal ultrasound. With continuous administration of ceftazidime, the abscess reduced and the nephrotic syndrome and IE resolved, and she was discharged from hospital. Discussion and Conclusion: The present patient presented with similar signs as those described in previous reports of concomitant nephrotic syndrome and severe infection caused by anti-tumor necrosis factor drugs and hepatic cirrhosis due to MTX. The present findings suggest that RA patients undergoing long-term treatment with MTX should be carefully observed due to the risk of hepatic cirrhosis.

### P3-081

#### Screening and Prophylaxis for Latent Tuberculosis and Hepatitis B Virus Infection, and Coverage Rate of Influenza and Pneumococcal Vaccinations in Patients Treated with Biologics

Haruko Ideguchi<sup>1</sup>, Rumiko Miyagi<sup>1</sup>, Takayoshi Soga<sup>2</sup>, Yoshiaki Ishigatsubo<sup>3</sup>

<sup>1</sup>Department of Rheumatology, National Hospital Organization Yokohama Medical Center, Yokohama, Japan, <sup>2</sup>Department of Rheumatology, Japanese Red Cross Shizuoka Hospital, Shizuoka, Japan, <sup>3</sup>Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Conflict of interest: None

[Methods] We retrospectively evaluated 26 men and 100 women treated with biologics agents between 8 July 2004 and 31 December 2013 in our department. [Results] Among the 126 patients who had been treated with biologics, 119 patients were treated with rheumatoid arthritis. As to tuberculosis, tuberculin skin test (TST) was tested in 115 patients (91.3%). Twenty seven patients (21.4%) were prescribed with prophylactic isoniazid therapy. As to hepatitis, HBs antigen, HBe and/or HBs antibody, HBV-DNA were tested in 126 (100%), 81 (64.3%), and 16 patients (12.7%) respectively. No patient was treated with entecavir. Influenza and pneumococcal vaccinations were done in 53 (42.1%) and 60 (47.6%) patients respectively. Three patients (2.4%) were prescribed with TMP-SMZ. [Conclusion] In our department, traditional TST had been done in most patients, and QFT and/or T-SPOT were yet done inadequately. Test for HBe and/or HBs antibody, HBV-DNA are not done insufficiently. Even though protection against influenza and pneumococcal infections by vaccinations has been recommended by the European League against Rheumatism, coverage rate of those vaccinations is very low in real world in Japan.

### P3-082

#### A Case with an Iliac Muscle Abscess Arising From Pyogenic Sacroiliitis During Treatment with Etanercept

Toshiaki Aizawa<sup>1</sup>, Seiya Miyamoto<sup>2</sup>, Yoichi Kataoka<sup>3</sup>, Masaaki Ogino<sup>4</sup>, Hiromi Morita<sup>5</sup>, Kunitaka Yang<sup>6</sup>, Wataru Watanabe<sup>7</sup>, Nobuhiro Ishizawa<sup>8</sup>, Kazuhiro Shoji<sup>9</sup>, Natsuo Konishi<sup>12</sup>, Hidetoshi Watanabe<sup>19</sup>, Takeshi Kashiwagura<sup>13</sup>, Masakazu Urayama<sup>15</sup>, Hiroki Ito<sup>14</sup>, Tsutomu Sakuraba<sup>16</sup>, Moto Kobayashi<sup>16</sup>, Keiji Kamo<sup>17</sup>, Hiroshi Aonuma<sup>18</sup>, Yusuke Sugimura<sup>11</sup>, Naohisa Miyakoshi<sup>10</sup>, Yoichi Shimada<sup>10</sup>

<sup>1</sup>Department of Orthopedic Surgery, Kitaakita Municipal Hospital, Akita, Japan, <sup>2</sup>Department of Orthopedic Surgery, Nakadori General Hospital, Akita, Japan, <sup>3</sup>Joto Orthopedic Clinic, Akita, Japan, <sup>4</sup>Department of Orthopedic Surgery, Koto General Hospital, Akita, Japan, <sup>5</sup>Morita Orthopedic Clinic, Akita, Japan, <sup>6</sup>Yan Orthopedic Clinic, Akita, Japan, <sup>7</sup>Department of Orthopedic Surgery, Honjo Daiichi Hospital, Akita, Japan, <sup>8</sup>Hujiwara Memorial Hospital, Akita, Japan, <sup>9</sup>Shoji Orthopedic Clinic, Akita, Japan, <sup>10</sup>Department of Orthopedic Surgery, Akita University Graduate School of Medicine, Akita, Japan, <sup>11</sup>South Akita Orthopedic Clinic, Akita, Japan, <sup>12</sup>Department of Orthopedic Surgery, Akita Kousei Medical Center, Akita, Japan, <sup>13</sup>Department of Rehabilitation Medicine, Akita City Hospital, Akita, Japan, <sup>14</sup>Department of Orthopedic Surgery, Yamamoto Kumiai General Hospital, Akita, Japan, <sup>15</sup>Department of Orthopedic Surgery, Ogachi Central Hospital, Akita, Japan, <sup>16</sup>Department of Orthopedic Surgery, Hiraka General Hospital, Akita, Japan, <sup>17</sup>Department of Orthopedic Surgery, Akita Rosai Hospital, Akita, Japan, <sup>18</sup>Department of Orthopedic Surgery, Kakunodate Municipal Hospital, Akita, Japan, <sup>19</sup>Watanabe Orthopedic Clinic, Akita, Japan

Conflict of interest: None

A 78-year-old woman with a 20-year history of rheumatoid arthritis, who had been treated with etanercept (ETN) for 7 years. In January 2014, fever and right hip pain occurred. Plain CT revealed no abnormalities in the thoracoabdominal area, except swelling of the right iliac muscle. Because of turbid urine and a white blood cell count of 137/HPF in the sediment, urinary tract infection was diagnosed. While ETN was discontinued, antibiotic therapy was administered, relieving her symptoms. Two months later, fever and right hip pain recurred. Plain CT revealed only swelling of the right iliac muscle, but the urine was not turbid. Blood culture grew *Staphylococcus aureus*. Contrast-enhanced CT revealed an ab-

cess under the right iliac musclet. Because the fever did not resolve even with antibiotic therapy, surgery was performed. While the iliac muscle was being subperiosteally detached, pus was ejected. The abscess was traced to the sacroiliac joint without an anterior sacroiliac ligament. It was assumed that infection had spread from the sacroiliac joint to the iliac muscle. The fever resolved immediately after surgery. When plain CT reveals swelling of the iliac muscle, abscess and pyogenic sacroiliitis should be included in a differential diagnosis.

### P3-083

#### The efficacy and safety of biologics to the highly elder RA patients

Ryutaro Matsumura, Hidekazu Futami, Takuya Nakazawa  
Center of Rheumatology, Allergy and Clinical Immunology, National Hospital Organization Chiba East National Hospital

Conflict of interest: Yes

[Objectives] With an increase of elder rheumatoid arthritis patients, and with the strict target of a medical treatment, biologics treatment was performed more often to the elder rheumatoid arthritis patient. However, there are few reports of biologics treatment to highly aged (>or= 75 years) RA patients, and efficacy and safety of biologics are not clear. [Methods] We examined the efficacy and the adverse events over one year for 17 RA patients (>or= 75 years) under biologics. [Results] The patients (male 2, female 15) were 75-85 years old (an average of 79.5 years old), disease duration were one to 24 years (an average of 10.9). Biologics treatment were infliximab 3, adalimumab 1, tocilizumab 1, abatacept 4, and golimumab 8 patients, and patient who can perform self injections was only one. Average DAS28-CRP at the introduction was 4.07 and improved to 2.20 after one year's biologics treatment. As SAE, fall fracture, congestive heart failure, cervical vertebrae RA change, the chest abnormal shade and renal insufficiency were observed in five patients. [Conclusion] Although efficacy of biologics for highly elder patients was equivalent to younger patients, cautions for the fall of a cardio-pulmonary function and infection should be required.

### P3-084

#### Incidence and Number of Reported Deaths due to Tuberculosis during Treatment with Ant-TNF Agents in Japan using Japanese Drug Event Report Database, JADER

Tomoshige Matsumoto  
Osaka Anti-Tuberculosis Association Osaka Hospital

Conflict of interest: None

[Objectives] Biologic agents have revolutionized the treatment of rheumatoid arthritis and other rheumatic diseases. The anti-tumor necrosis factor (TNF) inhibitors adalimumab, infliximab, and etanercept were listed in the ten top best-selling medications in 2012. Unfortunately, use of anti-TNF inhibitors has been reported to be associated with the development of tuberculosis (TB). [Methods] We evaluated the morbidity and mortality of TB patients treated with anti-TNF inhibitors, including infliximab, etanercept, adalimumab and golimumab, in Japan using the Japanese Drug Event Report Database (JADER). [Results] According to the JADER, from 2004 to 2012, TB developed in 388 patients (including redundant data) and 12 patients died. [Conclusion] These data suggest that considerable attention should be paid to preventing TB in patients treated with anti-TNF inhibitors.

### P3-085

#### The relationship between the results of drug induced lymphocyte stimulation test and the side effects of biologics

Takashi Ogasawara, Manabu Tanabe, Yoko Shimizu, Shinya Hirahara, Makiko Kimura, Masako Inagaki, Mutsuto Tateishi, Takashi Yamada  
Tokyo Metropolitan Ohtsuka Hospital

Conflict of interest: None

[Objectives] Several kinds of allergic side effects of biologics against arthropathy were happen in the patients with rheumatoid arthritis. Now we experienced two cases with such accidental events and have per-

formed DLST. [Methods] In the 67-years-old female with dyspnea and acute interstitial pneumonia after sixteen months prescription of eternalcept, DLST was performed using Chinese medicine and eternalcept. In the 73-years-old male case with severe injected site eruption caused by golimumab and apatacept, DLST was performed several biologics including gammaglobuline. The eruption suddenly appeared after two month intervals due to treating for his heart problems. [Results] In the first case, DLST were relatively positive in the Chinese medicine. Both of Eternalcept and arranged Eternalcept were negative in the test and we start to treat the patients with Eternalcept again after several month intervals. In the second case, the results of DLST were very complicated that the indexes of biologics such as Golimumab, Eternalcept, Apatacept, and gammaglobuline were controversial. [Conclusion] The effectiveness and meanings of DLST is very controversial and depends on the cases. We should analyze such reports and perform DLST in order to select the biologics best for such RA patients.

### P3-086

#### **Evaluation of serum Anti-Mullerian Hormone (AMH) levels in patients with RA after the TNF inhibitor administration**

Sakiko Isojima, Mayu Saito, Shinichiro Nishimi, Airi Nishimi, Nao Oguro, Yoko Miura, Sho Ishii, Shinya Seki, Takahiro Tokunaga, Masayu Umemura, Ryo Yanai, Hidekazu Furuya, Ryo Takahashi, Kuninobu Wakabayashi, Takeo Isozaki, Nobuyuki Yajima, Yusuke Miwa, Tsuyoshi Kasama

Division of Rheumatology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Background] Fertility is reduced in uncontrolled RA patients, although the reason is not well known. AMH levels have been recently used for an evaluation for the ovarian reserve, but there are few reports in RA. We reported preliminary data of serum AMH levels in RA patient in the last meeting. We evaluated serum AMH levels in with additional data. [Subjects and Method] Twelve RA female patients newly treated with the TNF inhibitor (IFX: 9, ETN: 3) were enrolled. Serum AMH levels and DAS28 were examined in 0, 14, 30, and 54 weeks after treatment. AMH levels were measured with ELISA assay (SRL Company) with preservation samples. As AMH is reported to be age-dependent, AMH Z scores for age were calculated with the recently reported references. [Result] 1) At 54 weeks, DAS28 were significantly decreased ( $4.6 \pm 0.4 \rightarrow 2.3 \pm 0.4$ ,  $p < 0.001$ ). 2) AMH levels were not different in both actual values and Z scores ( $p = 0.98, 0.97$ ). 3) After treatment, serum AMH level increased in some cases. At the starting time of the TNF inhibitor, patient-VAS was significantly lower in the case that increased than the group which decreased ( $p < 0.0001$ ) and tended to have a short contraction of a disease duration ( $p = 0.22$ ). [Conclusion] Serum AMH levels were not affected by the TNF inhibitor administration for RA patients.

### P3-087

#### **A case of muscular sarcoidosis triggered by golimumab in a patient of rheumatoid arthritis**

Hirotaaka Itoh, Sohei Funakoshi, Masaki Katayama  
Osaka Red Cross Hospital

Conflict of interest: None

A 49-year-old Japanese woman has been suffered rheumatoid arthritis since the year 2011. She started using golimumab 50 mg every month from April 2012 and achieved keeping remission. She suffered swelling, pain and itch sensation in lower legs since June 2014, and gradually the symptoms worsened and spread to both thighs with elevation of creatine kinase. She admitted to our hospital for careful examination, then the symptoms got better and the level of creatine kinase declined by stopping using golimumab. MRI examination of legs showed myositis and fasciitis, but the en bloc skin to muscle biopsy from the lower limb revealed granuloma in dermis, subcutaneous fat tissue and muscle. The level of angiotensin converting enzyme was high. Tuberculosis was denied and we diagnosed her illness as muscular sarcoidosis. No systemic involvement was observed. Anti-tumor necrosis factor-alpha antibody is beneficial for treatment of sarcoidosis, but on the other hand there are reports of

sarcoidosis as paradoxical reaction of tumor necrosis factor inhibitors. We report a first case of muscular sarcoidosis as the paradoxical reaction triggered by golimumab.

### P3-088

#### **The efficacy of ETN(25mg/Week) for elderly or long-term morbidity RA patients**

Manabu Shimizu<sup>1</sup>, Shu Saito<sup>2</sup>, Takao Ishii<sup>2</sup>, Takanobu Sumino<sup>2</sup>, Gen Suzuki<sup>2</sup>, Kenkou Yamada<sup>2</sup>, Gouki Kinoshita<sup>2</sup>, Taishi Hasegawa<sup>2</sup>

<sup>1</sup>Department of Orthopaedics Surgery, Higashi-matsuyama Municipal Hospital, <sup>2</sup>Department of Orthopaedics Surgery, Nihon University School of Medicine

Conflict of interest: None

[Objectives] Using of Etanercept (ETN) has Many variation. 50mg ETN has been shown to be effective in patients with rheumatoid arthritis (RA). However, the once-weekly administration of 25mg ETN (ETN-25mg/Week) has not been. This study is The efficacy of ETN (25mg/Week) for elderly patients without increasing the amount of Methotrexate (MTX) or long-term morbidity RA patients. [Methods] Ten patients (over 80 years or suffering from more than 20 years) has been treated by using ETN25mg/Week for more than 24 weeks (Man 3 Female 7). We evaluate the effect of ETN25mg/Week. [Results] 8 of 10 patients were keeping Low disease activity at 12week. No Patients must discontinue ETN in all of the period. But one patients with maintaining Low Disease activity for 24 weeks had to discontinue ETN by increasing  $\beta$ -D glucan. All patients were significantly improved DAS28-ESR in comparison with the previous administration and had been Low disease activity at the last observation. [Conclusion] The use of ETN25mg/Week is likely to be useful for elapsed RA patients more than 20 years from the onset with in recurrent or still have not been able to maintain a low disease activity, or 80 years or older without being able to receive aggressive arthritis treatment.

### P3-089

#### **Occult malignant tumors detected by screening tests for receiving biologic agents in rheumatoid arthritis patients**

Daiichiro Takahara, Yuya Takakubo, Akiko Sasaki, Yasushi Naganuma, Suran Yang, Junichi Okamoto, Hiroharu Oki, Tomoyuki Hirayama, Kan Sasaki, Michiaki Takagi

Department of Orthopaedic Surgery, Yamagata University Faculty of Medicine, Yamagata, Japan

Conflict of interest: None

[Objectives] The malignant neoplasm has been the leading cause of death in Japan since 1981. Biologic agents (BIO) have been still pointed out to relate with the occurrence or growth of malignant tumors. We investigated RA patients detected malignant tumors by screening tests for inducing BIO. [Methods] RA patients screened before inducing BIO were analyzed in our institute. Screening tests included blood and urine analyses and a computed tomography (CT) scanning. [Results] Occult malignant tumors have been found by screening tests for inducing BIO in four RA patients. The mean age at the time of finding malignant tumors was 68.3 year-old (52-80). The mean follow-up period after operation for malignant tumors was for 27.8 months (5-87). There were two lung cancers and one breast and bladder cancer. Two lung cancers and one breast cancer were detected by CT scanning. A bladder cancer was detected by an urine analysis and CT. Radical surgeries were performed in all cases and there were no recurrence in the latest follow-up. BIO has not been applied for all cases. [Conclusion] Malignant tumors may increase their arthritis as a paraneoplastic syndrome in RA patients. Rheumatologist should treat RA patients with occult malignant tumors in mind, especially in the application of BIOs.

### P3-090

#### **The long-term efficacy and safety of etanercept (ETN) in patients with elderly rheumatoid arthritis**

Shota Sakaguchi, Eiko Nishi, Yasufumi Kai, Hiroshi Kuroda, Toshihiko Hidaka

Institution of Rheumatology, Zenjinkai Shimin-no-Mori Hospital, Mi-

yazaki, Japan

Conflict of interest: None

We assessed the long-term efficacy and safety of etanercept (ETN) in patients with elderly rheumatoid arthritis (ERA) age 65 or over. 145 RA patients (74 patients were in ERA group and 71 were in non-ERA group) were administered ETN. Over the 1, 3 and 5-year treatment period using LOCF method, we evaluated responses to ETN therapy based on SDAI. The mean levels of SDAI in ERA group significantly decreased from 23.7 to 8.8 (1 year,  $p < 0.001$ ), 8.3 (3 years,  $p < 0.001$ ) and 8.0 (5 years,  $p < 0.001$ ), and in non-ERA group significantly decreased from 21.8 to 6.7 (1 year,  $p < 0.001$ ), 5.1 (3 years,  $p < 0.001$ ) and 5.3 (5 years,  $p < 0.001$ ). There were no significant changes between groups. Remission/low disease activity rates in ERA were achieved in 22%/70% (1 year), 27%/74% (3 years) and 30%/76% (5 years), and in non-ERA group 45%/83% (1 year), 51%/91% (3 years) and 49%/90% (5 years), respectively. The incidence of adverse events (AEs) and serious AEs were 45% and 23% in ERA group and 68% and 11% in non-ERA group, respectively. There were no significant changes between groups. These data indicate that long-term ETN therapy is safe and clinically effective for even older RA patients.

### P3-091

#### A report of development of miliary tuberculosis and non-tuberculous mycobacteria (NTM) after switching of biologics

Yoshiko Hashimoto<sup>1</sup>, Yasuhiro Tanaka<sup>2</sup>

<sup>1</sup>Division of Rheumatology, Fuji Toranomon Orthopedics Hospital, <sup>2</sup>Division of Orthopedic Surgery, Fuji Toranomon Orthopedics Hospital

Conflict of interest: None

(Case1) A-74-year-old female. She had been suffering from RA for 13 years. Under treatment with MTX and etanercept, bilateral total knee arthroplasty and right hip arthroplasty were performed. 3 months after switching from etanercept to infliximab with INH, she visited our hospital complaining of high fever and anorexia. Chest CT revealed miliary nodules in bilateral lungs. T-Spot-TB was positive, suggesting active pulmonary tuberculosis. She was treated with INH, RFP, EB and PZA. (Case2) A-43-year-old male. He had been suffering from right knee joint pain and swelling. In addition to the elevated serum levels of MMP-3 and CRP, existence of inflammatory joint fluid were suggestive of RA. Administration of MTX and infliximab with INH were effective. However, right joint swelling relapsed and serum CRP levels increased up to 7.46 mg/dl. Ten days after switching from infliximab to tocilizumab, he presented productive cough and hypoxia. Chest CT revealed miliary nodules in bilateral lungs. T-Spot-TB was negative, suggestive of NTM. He was treated with CAM, RFP and EBI. (Conclusion) Screening of mycobacteriosis is important when switching of biologics. Administration of INH with biologics does not always help prevent mycobacteriosis.

### P3-092

#### Listeria monocytogenes bacteremia in a patient with RA treated by etanercept: a case report

Yuto Hamada, Tamao Nakashita, Akira Jibatake, Kotaro Matsumoto, Akira Yoshida, Shinji Motojima  
Kameda Medical Center, Rheumatology and Allergy, Kamogawa, Japan

Conflict of interest: None

TNF-inhibitors including etanercept (ETN) make patients susceptible for intracellular pathogens such as *Mycobacterium tuberculosis* and *Salmonella*, due to suppression of activated macrophages. Here we report a case of *Listeria monocytogenes* bacteremia in patient with RA treated by etanercept (ETN). The patient is an 81-year-old woman with a history of 23 years of RA who underwent mitral valve replacement operation. She had been treated with 5 mg/week of MTX combined with 25 mg/week of ETN. She was admitted to a hospital because of dyspnea and fever for previous 1 week in July 2013. She was diagnosed as congestive heart failure and was treated by diuretics and NIPPV. Blood cultures on the day of admission were positive for *Listeria monocytogenes*. Because no vegetations were found on heart valves by UCG, she was treated as bacteremia

by aminobenzylpenicillin resulting in good outcome. This case suggests that ETN makes patients susceptible not only to TB but also *Listeria*. We have to be aware that the route of infection of *Listeria* is thought to be digestive tract and is tolerable to cold down to 4 degree C.

### P3-093

#### A case of acute tubulointerstitial nephritis and uveitis during the treatment with etanercept (ETN) for RA

Kotaro Matsumoto, Tamao Nakashita, Akira Jibatake, Akira Yoshida, Yuto Hamada, Shinji Motojima  
Kameda Medical Center, Rheumatology and Allergy, Kamogawa, Japan

Conflict of interest: None

We report a case of tubulointerstitial nephritis (TIN) combined with uveitis during the treatment with etanercept (ETN) for RA. The patient is a 61 year-old woman with RA whose onset was 1980, with stage 4 and class 2. Five mg/day of PSL and 6 mg/week of MTX had been administered. ETN, 25 mg/week, was started in July 2012 because of increases activity of RA. Anorexia developed in December 2012, and serum creatinine increased in January 2013 resulting in discontinuation of MTX. Renal function worsened thereafter, and renal biopsy was done in February 2013. Histological diagnosis was acute TIN with strong infiltration of polymorphonuclear leukocytes. The criteria of Sjogren's syndrome was not fulfilled, and ETN was discontinued because it might be related to TIN. PSL at the dose of 50 mg/day was started, and was gradually tapered to 15 mg/day when uveitis developed. Second renal biopsy was done which revealed mesangial proliferation and improved TIN, and continuation of PSL was judged to be necessary. DLST for ETN was done resulting in 239 % of SI, and ETN was thought to be the cause of the change in immune status which induced acute TIN and uveitis. It is difficult to decide whether this case is termed as TINU syndrome (TIN and uveitis) because of the presence of RA.

### P3-094

#### Development of organizing pneumonia in a patient with rheumatoid arthritis treated with etanercept

Sosuke Tsuji<sup>1</sup>, Yoshiro Horai<sup>1</sup>, Masataka Umeda<sup>1</sup>, Shoichi Fukui<sup>1</sup>, Ayako Nishino<sup>1</sup>, Takahisa Suzuki<sup>1</sup>, Yoshikazu Nakashima<sup>1</sup>, Tomohiro Koga<sup>1</sup>, Shin-ya Kawashiri<sup>1</sup>, Naoki Iwamoto<sup>1</sup>, Kunihiro Ichinose<sup>1</sup>, Yasuko Hirai<sup>1</sup>, Mami Tamai<sup>1</sup>, Hideki Nakamura<sup>1</sup>, Tomoki Origuchi<sup>2</sup>, Atsushi Kawakami<sup>1</sup>  
<sup>1</sup>Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University, Graduate School of Biomedical Sciences, Nagasaki, Japan, <sup>2</sup>Department of Rehabilitation Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Conflict of interest: None

A 77-year-old male was diagnosed with rheumatoid arthritis (RA) in March 2011. High-resolution computed tomography (CT) revealed slight ground-glass opacity in the lower lobes, which was thought to be inactive. We started 10 mg/day of prednisolone (PSL) in combination with 1000 mg/day salazosulfapyridine (SASP) and 1 mg/day of tacrolimus. After starting PSL, SASP and TAC, his symptoms improved slightly. However, polyarthralgia worsened again. Therefore, we started etanercept (ETN). After the start of ETN, his articular symptoms improved. However, a productive cough and slight fever developed about 6 months after the start of ETN. The CT chest revealed diffuse shadows and ground-glass opacities in the right lung. The administration of intravenous antibiotics was ineffective. The result of bronchoalveolar fluid analysis was compatible with organizing pneumonia (OP). Administration of ETN was discontinued. Steroid pulse therapy was followed by administration of 40 mg/day of PSL, which improved his respiratory condition. The clinical course was compatible with ETN-induced OP. OP should be considered in the differential diagnosis of RA patients treated with ETN presenting with acute pneumonia.

### P3-095

#### The safety and efficacy of combination therapy with abatacept and tacrolimus for rheumatoid arthritis

Hisako Eshiro, Naohide Takigawa, Muneki Abe, Atsuhiko Fukui

Conflict of interest: None

MTX is a first-line agent for RA. Discontinuation of MTX owing to complications like drug-induced pneumonia is not rare. We assessed the efficacy and safety of a combination therapy with ABT and TAC for RA with MTX discontinuation. [Methods] We examined 4 patients with a combination therapy observed for >3 months: 1 man, 3 women; average age, 61 (52–73) years; disease duration average, 9.7 (5–14) years; 2 Steinbrocker stage II, 2 stage III; all with functional class 2. PSL was a concomitant agent in 1 patient. One patient was biologics naïve; 3 switched (previous agent: infliximab, 2; adalimumab, 1). The causes for MTX discontinuation were pneumonia (2), lung cancer (1), and allergy to MTX (1). The average follow-up was 9 (3–18) months. EULAR improvement criteria, CRP, DAS28-CRP, and CDAI were compared between the introduction and last observation. Infection and glucose tolerance were assessed. [Result] The EULAR improvement criteria showed more than moderate improvement in all cases. On average, CRP 1.08→0.46 (P = 0.13), DAS28-CRP 3.88 → 2.75 (P < 0.05), and CDAI 19.45 → 9.05 (P < 0.05). Infection and glucose tolerance was not observed in all cases. [Conclusion] Combination therapy with ABT and TAC is useful for RA with discontinuation of MTX.

### P3-096

#### Comparison of the efficacy and safety of abatacept and adalimumab in elderly rheumatoid arthritis patients

Shin-ichiro Omura, Rei Ito, Toshiaki Miyamoto  
Seirei Hamamatsu General Hospital

Conflict of interest: None

[background] Many physicians think that abatacept (ABT) is more safety than other biological agents (Bio). However, the safety of high-risk patients, such as elderly people, is not examined. [Methods] We retrospectively analyzed 29 RA patients who were over 65 years old and received ABT (ABT group), and compared with 48 RA patients who were over 65 years old and received adalimumab (ADA group). [Results] ABT group were significantly older and fewer naïve patients, and had more pulmonary disease (P<0.05) than ADA group. Efficacy of ABT group were revealed that DAS28CRP4.0 (baseline)/2.71 (24weeks), DAS28ESR5.47/3.92, CDAI24/11.8, SDAI25.2/12.8, HAQ0.9/0.51. On the other hand, Efficacy of ADA were revealed that DAS28CRP3.77/1.96, DAS28ESR4.99/3.00, CDAI25.6/5.96, SDAI28.0/5.92, HAQ0.62/0.43. After all, ADA group was more efficacy than ABT group. In regard to hospitalized infections, two patients were hospitalized in ABT group and six patients in ADA group. We have seen statistically no significant difference between the groups. [Conclusion] ADA group was more efficacy than ABT group because of more naïve patients and concomitant MTX patients. In regard to hospitalized infection, ABT group was not fewer than ADA group. We can't always necessarily say that ABT was more safety than other Bio agents.

### P3-097

#### The efficacy of abatacept in patients with rheumatoid arthritis previously treated with tocilizumab

Hiroshi Kanazawa, Hiromitsu Takemori  
Department of Rheumatology, Aomori Prefectural Hospital, Aomori, Japan

Conflict of interest: None

Objectives: The objective of this study was to evaluate the efficacy of abatacept (ABT) in patients with rheumatoid arthritis (RA) previously treated with tocilizumab (TCZ). Methods: We performed a retrospective study of 32 RA patients who were treated with ABT for 48 weeks. Outcomes were compared between RA patients who were inappropriate for TCZ treatment (TCZ), TNF inhibitor treatment (TNFi), and biologic-naïve RA patients (naïve). Disease activity was assessed using SDAI and DAS28 (ESR). Results: Patient baseline characteristics (TCZ (6), TNFi (17), naïve (9)) as follows: mean age: 63, 62, 69, disease duration (years): 7.7, 9.4, 6.9, MTX use (%): 17, 59, 33, PSL use (%): 67, 65, 67. The

mean DAS28 and SDAI was at week 0, 24, 48 as follows: TCZ: 4.01→3.57→3.54, 14.78→10.75→9.73, TNFi: 4.29→3.43→3.41, 14.23→8.17→8.81, naïve: 4.6→3.12→2.91, 17.51→5.54→4.88. DAS28 and SDAI decreased from baseline after ABT treatment in each group. The mean  $\Delta$ DAS28 and  $\Delta$ SDAI was at week 48 as follows: TCZ: -0.48, -5.05, TNFi: -0.9, -5.92, naïve: -1.7, -12.63.  $\Delta$ DAS28 and  $\Delta$ SDAI did not change significantly in each group, but the change was tendency less in TCZ than naïve and TNFi. Conclusion: The present results confirm that ABT is tendency less effective to TCZ-IR than TNFi-IR or bio-naïve RA patients.

### P3-098

#### Usefulness of BIO Switch for poor responders to biologics–Abatacept (ABT) vs Tocilizumab (TCZ): observation study in clinical practice~

Toshiaki Miyamoto  
Department of Internal Medicine and Rheumatology, Seirei Hamamatsu General Hospital, Shizuoka, Japan

Conflict of interest: None

**Objective:** The JCR2014 and EULAR guidelines recommend ABT and TCZ as first-choice drugs similar to TNF inhibitors. However, there is no direct comparison study in Japan or overseas. The clinical usefulness of 24 weeks of ABT and TCZ treatments in RA patients responding poorly to biologics was retrospectively and comparatively investigated. **Methods:** Of the RA patients that were Bio Switched, 53 analyzable ABT-treated patients (A) and 24 analyzable TCZ-treated patients (T) were the subjects. In groups A/T, mean age was 64.7/53.6 years, mean duration of illness 146.0/103.6 months, and rate of MTX concomitant use was 52.8% (mean 9.9 mg/wk)/75.0% (mean 9.3 mg/wk). Baseline disease activity (DAS28CRP·CDAI) was not significantly different. Efficacy up to 24W of treatment following BIO treatment was investigated comparatively. **Results:** DAS remission rate at 24W in group A vs. group T was 33.3% vs. 46.7%, showing a high trend in group T. However CDAI was 10.3% vs. 0%, showing a high trend in group A. **Conclusion:** Clinical remission rate was higher in group T regarding DAS, but the reverse was true for CDAI. ABT but not TCZ, showed a correlation of DAS and CDAI. ABT and TCZ improved pain, however, swelling remained with TCZ indicating poor improvement of arthritis.

### P3-099

#### Transition of Epstein-Barr Virus-DNA in the Plasma of Patients with Rheumatoid Arthritis during Administration of Abatacept

Yoshihiro Hishitani<sup>1,2</sup>, Hitoshi Deguchi<sup>1</sup>  
<sup>1</sup>Kinki Central Hospital, <sup>2</sup>Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Graduate School of Medicine, Osaka University

Conflict of interest: None

[Objectives] Whether it is safe or not to treat RA patients with positive plasma Epstein-Barr virus (EBV)-DNA is not definitely clarified yet. Especially, how abatacept (ABT) influence the level of plasma EBV-DNA has not been reported. [Methods] Retrospective case series report. With informed consent of the patients, ABT was administered to RA patients with known positive status of plasma EBV-DNA. Plasma EBV-DNA level was measured on the decision of each doctor. [Results] (Case1) 64 years old, female. Disease duration was 20 years. She showed insufficient response to methotrexate (MTX). During 15 months, plasma EBV-DNA level stayed low. Hyperplasia of lymph node was pointed out in this patient, but no progression was seen (Case2) 70 years old, male. Disease duration was 7 years. He showed insufficient response to MTX. ABT was effective at first but was stopped at 6 months due to loss of efficacy. Plasma EBV-DNA level stayed low. But diffused eruptions were seen from 4 months after initiation of ABT. (Case 3) 64 years old, female. Disease duration was 16 years. She showed insufficient response to MTX, infliximab, and tocilizumab. During 29 months, plasma EBV-DNA level stayed low. [Conclusion] Plasma EBV-DNA level stayed low during administration of ABT for the patients with RA.



### P3-100

#### Efficacy and safety of Abatacept for the elderly patients with rheumatoid arthritis over sixty five years old

Shigeshi Mori<sup>1</sup>, Hiraku Kikuchi<sup>2</sup>, Wataru Shimada<sup>2</sup>, Yasunori Itou<sup>2</sup>, Satoshi Soen<sup>3</sup>, Masato Kamiya<sup>3</sup>, Kenji Miki<sup>1</sup>, Noboru Matsukura<sup>4</sup>, Masakatsu Saitoh<sup>4</sup>, Masao Akagi<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Kindai University Faculty of Medicine, Osaka, Japan, <sup>2</sup>Department of Orthopedic Surgery, Sakai Hospital Kinki University Faculty of Medicine, Osaka, Japan, <sup>3</sup>Department of Orthopedic Surgery, Nara Hospital Kinki University Faculty of Medicine, Osaka, Japan, <sup>4</sup>Department of Orthopedic Surgery, PL Hospital, Osaka, Japan

Conflict of interest: None

[Objectives] Evaluation of Abatacept (ABT) for the treatment of rheumatoid arthritis (RA) in elderly patients [Methods] ABT was administered for 47 RA patients over 65 years old with no active infectious or pulmonary disease in 4 affiliated hospitals of Kindai university since July 2012. We evaluated the dosage of ABT, the efficacy (patient's VAS and DAS-28 CRP) and the safety (continuity and adverse effect) during 24 weeks period. [Results] The initial dosage of ABT was 250mg for 18 and 500mg for 29 patients. The mean patient's VAS and DAS-28CRP improved from 64.3 to 29.5 and 4.8 to 2.4 respectively. 63% of good and 23.7% of moderate response were observed from the EULAR response criteria. 41.7% of the 500mg and 64.7% of the 250mg group achieved the remission, and 47% and 64.7% of each patient groups corresponded within low disease activity. Escalation of ABT was necessary for 27% of the 250mg group, and overall continuation ratio was 80.9%. Lack of efficacy (4 cases) and adverse effects (three pneumonias and a skin eruption) were observed as the reasons for discontinuation. [Conclusion] The small dosage of ABT could be a good option for the treatment of RA in the elderly patients.

### P3-101

#### Evaluation of RA patients treated with Abatacept

Katsumitsu Arai<sup>1</sup>, Junya Ajiro<sup>2</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Niigata Prefectural Central Hospital, Niigata, Japan, <sup>2</sup>Department of Internal Medicine, Niigata Prefectural Central Hospital, Niigata, Japan

Conflict of interest: None

[Objectives] To evaluate the effect of Abatacept for patients with rheumatoid arthritis (RA), who were not be controlled with anti-TNF biologics or Tocilizumab, or who could not be treated with MTX. [Methods] Fifteen RA female patients were evaluated. Their age was 56±10 (mean±SD) and disease duration was 14±9.2. Seven cases were not be controlled with anti-TNF biologics or Tocilizumab. Eight cases could not be treated with MTX. Before the treatment with Abatacept, DAS28 ESR score was 5.4±1.4, and DAS28CRP score was 4.7±1.4. Survival curve was evaluated with Kaplan-Meier method. The reasons of discontinuations were checked. Efficacy and safety outcomes were checked at every visit. [Results] Survival rate was 75% at 6 months, 75% at 1 year, 60% at 2 year, and 50% at 3 year. The reasons of discontinuations were as follows: lack of efficacy was 5 cases, the worse of interstitial pneumonia was 1 case, spinal cord injury due to fall down was 1 case. About disease activity, DAS28CRP with LOCF was 3.5±1.6 at 6 months, 3.5±1.6 at 1 year, and 3.8±1.8 at 2 year. On the other hand, DAS28CRP without LOCF at same check point was 2.8±0.4, 2.6±0.6, and 2.6±0.5. Five cases were low disease activity at the point of evaluation. [Conclusion] We have verified the effect of Abatacept in serious cases with RA.

### P3-102

#### Clinical Evaluation of Abatacept(ABT) SC for Rheumatoid Arthritis (RA) at Week 24 in A Single-Center Trial

Keio Ayabe, Takumi Wakisaka, Keiko Sonobe  
Keiyu Orthopedic Hospital

Conflict of interest: None

Objectives: Clinical evaluation of the result of ABT SC for at

Week24 Methods: 25 patients who received ABT for at least 24 weeks were included in the efficacy analysis that was based on disease activity, for example, DAS28CRP, DAS28ESR, CDAI, SDAI and changes in laboratory data. In addition, when the medication was switched to ABT from other biological products, it was tried to give instant result by administering the intra-articular injection of steroids. Results: The specific patients are listed below; 3men and 22women; mean age was 71.2years old; average duration of disease was 14.8years; 4 biologics-naïve patients and 21switch patints. Mean DAS28CRP scores decreased from 4.3 at Week0 to at 2.1 Week24 and 14 patients (56%) had remission. Mean DAS28CRP scores of 12 switchers who changed other biological products to ABT decreased 3.9 at Week0 to 1.9 at Week 24 and 7 patients (58.3%) had remission. Aiso, 11 patients (91.7%) had low disease activity. This result show the significantly high effectiveness of ABT; however, at the same time, this is caused by administering the inter-articular injection of steroids when the medication was switched to ABT SC from other biological products. Conclusion: Bsed on the clinical evaluation at Week 24, ABT had noy only high effectiveness but also instant results.

### P3-103

#### Pain degree evaluation of subcutaneous injection therapy in patients with Rheumatoid Arthritis

Hiroshi Oka, Mitsuyuki Nakamura, Akiko Aoki

Hachioji Medical Center, Tokyo Medical University, Tokyo, Japan

Conflict of interest: Yes

[Objectives] To evaluate pain degree of subcutaneous injection therapy by patients' questionnaires. [Methods] Patients' questionnaires were categorized 5 degree scoring system, which means from no pain (zero point), a little pain (one point), moderate pain (two point), severe pain (three point), to maximum pain (four point). [Results] 38 patients were selected among 74 biologics user of RA. Average pain degree were, Etenercept: 2.57 (N=14), Golimumab: 1.90 (N=14), Tocirizab: 2.00 (N=7), Ceterizab: 2.20 (N=4), Adalizab: 3.50 (N=2), Abatacept: 0.00 (N=1), respectively. [Conclusion] Golimumab and Tocirizab are small pain degree group whereas Adalimumab and Etenercept are large pain degree group in our study. Pain degree may relay on pH, needle size, additive materials and so on.

### P3-104

#### Subcutaneous administration of Abatacept is effective and safe without combination of MTX treatment

Yukie Saio

Hashima City Hospital

Conflict of interest: None

[Objectives] Abatacept (ABT) is the only biological agent targeting T-cells for Rheumatoid arthritis. Since August 2014, Subcutaneous administration of ABT (ABT-sc) has been approved. In this study, we analyzed the effectiveness and safety of ABT-sc. [Methods] The patients who had administered ABT-sc over than 12 weeks were analyzed for effectiveness, safety, persistence rate, effectiveness without MTX condition. Age: 77.3 y.o., M:F=2:4, Average disease duration: 10.2 year, Pre-administration status of ABT-sc treatment; Bio naïve: 1, Switching: 5, MTX treatment; with MTX: 2, without MTX: 4. Average DAS28-CRP4 (DAS28): 5.3. [Results] After ABT-sc treatment DAS28 was improved to 3.72. In ABT-sc without MTX cases, DAS28 was improved from 5.9 (before treatment) to 4.1 after treatment. Although adverse event (pneumonia) was observed in 1 case, persistent rate of ABT-sc therapy was 100% because the treatment was resumed after pneumonia was cured. [Conclusion] In this study, we showed the effectiveness and safety of ABT-sc. We should confirm the data by increasing the number of the cases.

### P3-105

#### The effects of biologics for rheumatoid arthritis patients treated with maintenance hemodialysis

Mayuko Tsukida, Masayasu Ando, Takako Harigai, Keiko Kobatake, Hiroaki Yoshida, Satsuki Kobayashi, Takayuki Matsumoto, Tatsuhiko

Sakamoto, Kazue Ueki  
Toho Hospital

Conflict of interest: None

[Objectives] For the treatment of rheumatoid arthritis (RA), effectiveness of methotrexate (MTX) use was established. However, if patients have renal failure, MTX use was strongly restricted. Four cases of RA patients, receiving maintenance hemodialysis, were treated with several biologics. [Methods] Patients were two male and two female, average age of 70±6.2 years old. Their DAS28CRP before biologic treatment was 5.6±1.3. X-ray evaluation were stage IV in three cases. All patients were first treated with abatacept. [Results] One patients responded well for abatacept treatment. One case achieved low disease activity with abatacept therapy, however, resulted in second failure and biologics was changed to golimumab and remission was obtained. Third case was suffered from bacterial pneumonia after the initiation of abatacept therapy and treated with tacrolimus. The final case showed no effect with abatacept. Biologics were changed to golimumab with remitted effects and finally responded to etanercept. [Conclusion] Biologics could be a reasonable choice for RA patients receiving hemodialysis. Patients with renal failure were in high risk for infectious diseases. The strict evaluation of tuberculosis, hepatitis, lung diseases is necessary before the initiation of biologic therapy.

### P3-106

#### **Abatacept therapy improved knee joint damage in patients with rheumatoid arthritis: a case report**

Kenji Kobayashi, Isao Matsushita, Hiraku Motomura, Tomoatsu Kimura  
Department of Orthopaedic Surgery, University of Toyama

Conflict of interest: None

[Case] We started abatacept therapy for a 48 years old female with rheumatoid arthritis, who uncontrolled severe pain and swelling at right knee with oral methotrexate and prednisolone. A year abatacept therapy improved erythrocyte sedimentation rate (ESR) for a hour from 29 to 14mm, C reactive protein (CRP) from 2.59 to 0.05mg/dl, matrix metalloproteinase-3 (MMP-3) from 653.7 to 34.7 ng/ml, DAS28-ESR from 4.59 to 2.59, DAS28-CRP from 4.65 to 2.59, HAQ from 1.0 to 0.5. Moreover, pre-existing right knee with radiographic damage of Larsen grade II showed replacement of subchondral bone structure. [Conclusion] We reported a patient who could show improvement of radiographic joint damage of knee joint during abatacept therapy. It has been reported that repair of damage in weigh bearing joint, especially hip and knee joint, is difficult. Low grade of joint damage at the abatacept administration and tight control of disease activity may be associated with radiographic healing of knee joint damage.

### P3-107

#### **Abatacept without methotrexate was safe and effective in a patient with rheumatoid arthritis and inadequate responses/tolerances to etanercept and tocilizumab: A case report**

Naohiro Sugitani, Akira Nishino, Tsuyoshi Kobashigawa, Masanori Hanaoka, Yuko Okamoto, Daisuke Hoshi, Hisae Ichida, Yasuhiro Katsumata, Yasushi Kawaguchi, Hisashi Yamanaka  
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

**Case:** A 80-year-old female with 2 years history of usual idiopathic pneumonitis (UIP). According to her polyarthritis, elevations of CRP, ESR, Anti-CCP antibody, RF and MMP-3, she was diagnosed as having an early rheumatoid arthritis (RA) with preceding UIP. Considering her IP, prednisolone (PSL) and sulfasalazine (SSZ) were selected, not methotrexate (MTX). But the polyarthritis got worse. The applied of PSL was gradually increased to 20 mg/day. 1 year before, as the RA activity was not improved, etanercept (ETN) was added on. But IP got worse. PSL alone therapy was performed and H0T was introduced. The tapering PSL dose down got worse the polyarthritis. And tocilizumab (TCZ) was introduced. But it was not effective. The applied of PSL could not be reduced

under 15 mg/day. 7 months before, switching from TCZ to Abatacept (ABT) was performed efficacy for the arthritis. And the applied of PSL was gradually decreased to 8 mg/day. After that, she was uninfected and IP was not worse. **Clinical Significance:** The use of ABT was effective in bio-naïve patients, compared with in bio-switched to ABT patients. The data about the availability of the third-biologic are very few in number. In this case, though the use of ETN and TCZ got inadequate response, the use of ABT as third-biologic show effective.

### P3-108

#### **Abatacept-induced large-vessel vasculitis in a case of rheumatoid vasculitis**

Shoko Iga, Takeshi Kusuda, Takumi Matsumoto, Takahiko Sugihara  
Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan

Conflict of interest: None

[Case] A 78-year-old woman with a history of RA developed interstitial pneumonia, digital infarction, and purpura on March 2011. Skin biopsy confirmed leukocytoclastic vasculitis. High-dose of prednisolone (PSL) was initiated, and tacrolimus and etanercept were added. On November 2012, abatacept (ABT) was started because of relapse of RA, and DAS28-remission was maintained by ABT and low dose of PSL. On August 2013, she developed fever, and was admitted to our hospital 13 days after a last injection of ABT. Antibiotics were administered empirically for 1 week, but her body temperature remained high with elevation of CRP (13mg/dl-19mg/dl). Contrast-enhanced CT demonstrated wall thickening of the ascending aorta with extension to the abdominal aorta. PET/CT showed increased tracer uptake in the same area. She was diagnosed with large-vessel vasculitis (LVV). Interestingly, she became afebrile 24 days after the last injection, even though the dose of PSL was not increased. CRP level became normal on day 36, and we confirmed improvement of CT findings on day 49. [Discussion] We described the first case of LVV developing during ABT therapy. Recent reports have suggested that TNF inhibitors may induce LVV. Our case suggests an association between the onset of LVV and ABT therapy.

### P3-109

#### **A case of ulcerative colitis in a patient with rheumatoid arthritis during abatacept therapy**

Ryutaro Yamazaki, Kazuhiro Kurasawa, Aya Tanaka, Harutsugu Okada, Satoko Arai, Takayoshi Owada, Reika Maezawa  
Department of Pulmonary Medicine and Clinical Immunology, Dokkyo Medical University

Conflict of interest: None

We report a case of ulcerative colitis (UC) in a patient with rheumatoid arthritis (RA) during abatacept (ABT) therapy. Patient was a 60-year-old Japanese male patient with a seven year history of RA, and had been treated by infliximab and adalimumab, tocilizumab in addition to methotrexate (MTX) and prednisolone (PSL). Because of insufficient treatment by TNF inhibitors and tocilizumab, abatacept was added to MTX 16mg/week and PSL 6mg/day, and induced clinical remission and decreased to dosage of PSL 2mg/d. About 1 year after starting ABT, he had severe diarrhea, persistent weight loss and undernutrition. Stool search for bacteria, ova and parasites yielded negative results. Colonoscopy and histopathology were performed, and revealed UC. Oral mesalamine therapy was started at a dose of 4 g/day, and granulocyte apheresis and PSL60mg/day were added with discontinuation of ABT and MTX. To the best of our knowledge, only 4 cases with UC in RA patient during ABT therapy have been reported to date. UC in RA patient during ABT therapy is infrequent, but clinicians must pay attention to UC in RA patients with persistent gastrointestinal symptoms.

### P3-110

#### **Evaluating efficacy of tofacitinib in patients with rheumatoid arthritis**

Shusuke Ota, Yoshiaki Tsuboi, Yasuyoshi Okamoto  
Shizuoka Medical Center, National Hospital Organization, Shizuoka, Japan

Conflict of interest: None

[Introduction] The purpose of this study was to analyze the efficacy and safety of tofacitinib (TOF) in patients with rheumatoid arthritis (RA). [Materials and Methods] A retrospective chart review was conducted of patients with RA treated with TOF between October 2013 and October 2014. A total of 10 patients were identified (2 males and 8 females; mean age, 70.0±7.2 years, ranged from 61 to 83 years). The efficacy was assessed by DAS28-ESR, CDAI, and SDAI. [Results] At 4 weeks after TOF treatment, six patients achieved a moderate response (DAS28-ESR, 5.9±5.4 to 4.3±0.8; CDAI, 30.5±10.1 to 16.1±12.5; SDAI, 28.6±11.0 to 15.0±10.4). At 24 weeks after TOF treatment, patient-VAS, doctor-VAS, tender and swollen joint counts and mHAQ were significantly improved, however rheumatoid factor and CRP were not significantly improved. Six patients (60%) could continue the TOF treatment over 24 weeks. Two patients exhibited adverse events (subcutaneous infection in 2 patients, diarrhea in a patient). [Conclusion] TOF treatment demonstrated efficacy in patients with rheumatoid arthritis after inadequate response to the other biologics or MTX. Patients previously treated against infection had exhibited high frequencies of adverse events, especially recurrent of infection, during the TOF treatment.

### P3-111

#### Our experience of Tofacitinib for uncontrolled rheumatoid arthritis

Yasunori Itoh, Wataru Shimada, Hiraku Kikuchi  
Department of Orthopaedic Surgery, Sakai Hospital, Kindai University  
Faculty of Medicine, Osaka, Japan

Conflict of interest: None

[Aims and Methods] Until September 2014, we used Tofacitinib for 5 uncontrolled RA (male: 2 female: 3. average age: 62.8 years old, average weight: 57.0 kg, average disease period: 12.0 years), and investigated patients-background, effectiveness, continuation rate, serious side effect. [Results] Patients-background was as follow. Prednisolone (PSL) dose: 0-10mg/day (average dose: 6mg/day). MTX dose: 8-10mg/week. Biological agent naïve: 20%, switch 80%. Steinbrocker stage1: 20%, stage2: 20%, stage4: 60%. Starting dose of Tofacitinib was as follow. 10mg/day: 40%, 5mg/day: 40%, 5mg/every other day: 20%. When we used Tofacitinib, we stopped MTX in all cases. Effectiveness was that Tofacitinib improved patient VAS (77→23), doctor VAS (70→28), DAS28-CRP (5.87→2.79), SDAI (41.3→8.4), CDAI (38.7→7.5) in two weeks and improved KL-6 (637→389) in four weeks. MMP-3 and anti-CCP antibody and CARF showed no remarkable change in four weeks. The twelve weeks continuation rate of Tofacitinib was 60%. All the reasons to stop Tofacitinib were intention of the patients. The particularly side effect did not appear during this period. [Conclusion] Our results indicate that Tofacitinib for adult uncontrolled RA is effective. In addition, we experienced RA that controlled by the half dose of Tofacitinib.

### P3-112

#### Efficacy and safety of tofacitinib in patients with rheumatoid arthritis at Sagamihara National Hospital

Kanako Iwata<sup>1</sup>, Toshihiro Matsui<sup>2</sup>, Koichiro Horie<sup>2</sup>, Hidefumi Fukuda<sup>2</sup>, Hirotaka Tsuno<sup>2</sup>, Hideki Ogihara<sup>2</sup>, Misato Kawakami<sup>2</sup>, Atsushi Hashimoto<sup>2</sup>, Akiko Komiya<sup>3</sup>, Shigeto Tohma<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, National Hospital Organization(NHO), <sup>2</sup>Department of Rheumatology, Sagamihara National Hospital, NHO, <sup>3</sup>Department of Clinical Laboratory, Sagamihara National Hospital, NHO

Conflict of interest: None

[Objectives] To analyze the efficacy and safety of tofacitinib (TOF) in patients with rheumatoid arthritis (RA) at our hospital. [Patients] Study-1: Seventeen patients who were given TOF after marketing. Study-2: Four patients who discontinued TOF because of decreasing their disease activity. [Results] Study-1: Thirteen patients used steroid and three patients used MTX, combined with TOF. Mean CDAI significantly decreased from 19.10 (at baseline) to 10.56 (after 12 weeks) and 9.04 (after 24weeks). Two patients discontinued TOF because of the lack of drug

effect and liver dysfunction. Herpes Zoster did not be found in any patient after marketing despite a high incidence during the clinical trial. Study-2: Two patients discontinued TOF after having been in remission for more than 2 years and they still maintain remission. A patient who discontinued TOF after having been in remission during 1 year increased doses of MTX without a re-administration of TOF because of a RA flare. [Conclusion] We found the efficacy and safety of TOF. Discontinuation of TOF after keeping remission with a certain period of time may be able in some patients.

### P3-113

#### Tofacitinib was effective in a refractory RA patient with pleuritis and eosinophilia

Reika Maezawa, Kazuhiro Kurasawa, Ayae Tanaka, Ryutaro Yamazaki, Harutsugu Okada, Satoko Arai, Takayoshi Owada  
Pulmonary Medicine and Clinical Immunology, Dokkyo Medical University, Tochigi, Japan

Conflict of interest: None

We report a case of RA patients with pleuritis and eosinophilia who were resistant to therapy with glucocorticoid, methotrexate and tocilizumab/ TNF inhibitor, but successfully treated with tofacitinib. 47 year-old woman was admitted to our hospital because of arthritis and pleuritis. She felt joint pain 3 months before admission, 1 month later she developed a cough, visited home doctor, received chest radiograph that revealed pleural effusion and was referred to our hospital. On admission, she had polyarthritis (DAS28-CRP; 7.8), pleuritis and eosinophilia (10716/mL). Biopsy samples taken by thoracoscopic examination showed marked infiltration of plasma cells, lymphocytes and eosinophils, palisade arrangement of histiocytes, which was compatible with rheumatoid pleuritis. She was treated with prednisolone (PSL) (50mg/day) that improved arthritis, pleuritis and eosinophilia. During tapering of PSL dose, she developed arthritis and received MTX and tocilizumab. This treatment failed to improve her condition. She was then treated with certolizumab that also failed. Then, tofacitinib was given, which improved her condition and laboratory findings. This case demonstrates effectiveness of tofacitinib on refractory RA with extra-articular manifestations.

### P3-114

#### The effect on changing to abatacept from the other biologics for the patients with rheumatoid arthritis (RA) complicated with systemic lupus erythematosus (SLE) (3rd report)

Shintaro Yano, Hiroshi Ideura, Masahiko Shinohara  
Maebashi Hirosegawa Clinic

Conflict of interest: Yes

[Objectives] Abatacept is known as an agent inhibits the costimulation of T cells. This study examined the effect on abatacept for the RA patients complicated with SLE. [Methods] Abatacept (500mg/4-6w) was administered to 4 RA patients (male: 1, female: 3, age: 25-71) complicated with SLE who have had inadequate responses to the other biologics (infliximab: 1, etanercept: 1, adalimumab: 1, tocilizumab: 1) And we examined the change in clinical symptoms and immune-serological test data such as CH50, anti-DNA antibody, CRP, MMP-3, and so on. [Results] Mean administration period of abatacept was 37months. In all patients, not only activity of RA was controlled well but an improvement in the immuno-serological test data was observed. In one patient, MTX, prednisolone and NSAIDs were able to be stopped administering. In the other patient, the administration of MTX could be stopped. And in the other patient except for the former two patients, an improvement of the value of CH50 that was worsened when the administration of abatacept was interrupted due to cutaneous infection was observed. No side effect was observed in the patients undergoing abatacept therapy. [Conclusion] Abatacept seemed to be a useful agent for RA patients complicated with SLE.

### P3-115

#### Control of regulatory T cells by agents affecting T cell signaling

Shinji Maeda, Tomoyo Maeda, Shinya Tamechika, Taio Naniwa, Akio

Niimi  
Department of Respiratory Medicine, Allergy and Clinical Immunology,  
Nagoya City University School Medical Sciences

Conflict of interest: None

[Objectives] Regulatory T cells (Tregs) play an important role in self-tolerance, whereas various inflammatory conditions, such as rheumatoid arthritis (RA), attenuate the suppressive function. The purpose of this study is to clarify the modulation of Tregs by agents affecting T cell signaling, providing a basis for novel therapeutic approach for immunological remission. [Methods] We have examined the change of phenotypes and the amount of circulating Tregs in human (RA) and mice (BALB/c, Collagen antibody induced arthritis, CAIA) in vivo, and in vitro culture of human PBMCs, by agents affecting T cell signaling. [Results] In mice, Tregs are increased by mTOR inhibitor (Everolimus) and IL-2CAc (IL-2 cytokine/mL-2 antibody (JES6-1) complexes) in mice. Furthermore, maximum arthritis severity (CAIA) are significantly attenuated by IL-2CAc. In humans with RA, after 4wks CTLA-4-Ig (Abatacept) therapy, the ratio of resting Tregs (CD45A<sup>high</sup> CD25<sup>low</sup>) in CD4<sup>+</sup> T cells significantly increased, whereas activated Tregs was decreased. Similar changes are observed in vitro PBMC culture systems only on the presence of anti-CD3Abs. [Conclusion] Altering T cell signaling, in vivo, using various agents can control Tregs, and may cause self immune-tolerance in arthritis patients.

### P3-116

#### The efficacy and safety of Tofacitinib for the patients with Rheumatoid arthritis

Kiyoshi Matsui, Kota Azuma, Takeo Abe, Chie Ogita, Yuichi Yokoyama, Tetsuya Furukawa, Takahiro Yoshikawa, Takuya Hino, Atsushi Saito, Aki Nishioka, Masahiro Sekiguchi, Naoto Azuma, Masayasu Kitano, Shinichiro Tsunoda, Hajime Sano  
Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine

Conflict of interest: Yes

[Objectives] Tofacitinib is the new oral JAK inhibitor that is administered to biologics-resistant and MTX-resistant patients in rheumatoid arthritis. This study aims to examine the clinical efficacy, safety and the number of subpopulation of lymphocytes after 12 weeks in administration of Tofacitinib. [Methods] We examined 13 patients (4 males and 9 females, mean age=53.3 yr, average DAS28 (ESR)  $5.42 \pm 1.16$ , average SDAI  $28.8 \pm 10.31$ ) in our hospital. We measured DAS28 (ESR), SDAI and the numbers of lymphocytes, T cells and NK cells at week 0,4 and 12 after treatment. [Results] The remission at 12 week was achieved in 1 case of 9 patients, and Low activity was achieved in 5 cases. 3 cases had side effects of influenza, cellulitis or herpes simplex. The number of WBC was none under  $3000/\text{mm}^3$  of 10 cases. Only 1 case was  $829/\text{mm}^3$  of lymphocyte under  $1000/\text{mm}^3$ . No case was under  $500/\text{mm}^3$  of T cells and under  $50/\text{mm}^3$  of NK cells after treatment. [Conclusion] The efficacy of tofacitinib treatment is slowly increased at week 12. The safety of tofacitinib treatment was none of lethal side effect at week 12, because of no case of rapidly decreased the number of WBC and lymphocytes (T cells and NK cells).

### P3-117

#### Assessment of Patients Background and Early Result of 23 RA Patients Treated with Tofacitinib (TOF) ~ SWEET Cohort ~

Yoshihisa Nasu<sup>1</sup>, Masamitsu Natsumeda<sup>2</sup>, Koji Takasugi<sup>2</sup>, Misuzu Yamashita<sup>2</sup>, Kazuhiko Ezawa<sup>2</sup>, Wataru Yamamoto<sup>3</sup>, Keiichiro Nishida<sup>4</sup>  
<sup>1</sup>Department of Orthopaedic Surgery, Center of Rheumatology, Kurashiki Sweet Hospital, Kurashiki, Japan, <sup>2</sup>Department of Internal Medicine, Center of Rheumatology, Kurashiki Sweet Hospital, Kurashiki, Japan, <sup>3</sup>Department of Clinical Information Management, Kurashiki Sweet Hospital, Kurashiki, Japan, <sup>4</sup>Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Conflict of interest: None

[Objectives] TOF had been approved in Nov 2012 in US and Mar 2013 in Japan however, CHMP is pending approval of TOF in Europe due to its balance of risk and benefit. To evaluate efficacy and safety in Japanese patients at daily clinical setting, 23 RA patients treated with TOF at our center is evaluated. [Methods] Data from 23 RA patients treated with TOF through Jan 2014 to Oct 2014 are re-evaluated their clinical background, DAS28, and the other clinical values by 24 weeks. [Results] Many of patients are refractory to MTX and several biologics. DAS28-ESR improved from 5.3 to 4.8, 3.4, and 3.1 at W4, W12, and W24 respectively. There is a significant improvement in DAS28-ESR after 8 weeks of TOF treatment. Adverse events during the 24 weeks include one herpes zoster, three mycoplasma infections, one leukopenia, and one sepsis. [Conclusion] Although our regimen is similar to ORAL-mono, patients' background is totally different from the clinical study setting. Despite its high efficacy, there is high risk of infectious adverse events. As long as safety management is tightly controlled, TOF could be a highly efficacious drug for patients refractory or intolerant to MTX and biologic DMARDs

### P3-118

#### Long Term Results of Inhibition of Radiographic Joint Damage Progression in Small, Medium and Large Joints in Patients with Active Rheumatoid Arthritis Inadequate Response to disease-modifying Antirheumatic Drugs Treated with Tofacitinib Monotherapy

Kou Katayama<sup>1</sup>, Satomi Abe<sup>2</sup>, Tamotsu Kamishima<sup>3</sup>  
<sup>1</sup>Katayama Orthopedic Rheumatology Clinic, <sup>2</sup>Department of Orthopedic Surgery, Asahikawa Medical University, <sup>3</sup>Faculty of Health Science, Hokkaido University

Conflict of interest: None

[Objectives] To analyze inhibitory effects on progression of joint damage in small joints (1, 4 years) and medium and large (M-L) joints (4 years) treated with tofacitinib mono-therapy (10mg BID) in eight patients with active rheumatoid arthritis inadequate response to disease-modifying antirheumatic drugs (DMARD). [Methods] The modified total sharp score (mTSS) was assessed to find small joint destruction. Twelve M-L joints (bilateral elbow, shoulder, hip, knee, ankle, and subtalar joints) were radiographically assessed by the Larsen method (Grade 0-5). Wilcoxon test was used for the statistical analysis. [Results]  $\Delta$ mTSS/year after tofacitinib treatment was significantly decreased from 22.1 (baseline) to 3.93 (median: -1.1) (after 1 year,  $p < 0.01$ ), and 3.03 (median: -0.45) (after 4 year,  $p < 0.01$ ). Only one patient with severe MRI osteitis in hand progressed joint destruction resistant to the therapy. Mean Larsen score of M-L joints from baseline (1.29) to the last observation (1.31) did not have significant changed. Atlant-axial subluxation occurred in 4 patients did not progress during tofacitinib therapy. [Conclusion] Progression of small and M-L joints in patients with active rheumatoid arthritis inadequate response to DMARD was effectively inhibited by tofacitinib monotherapy.

### P3-119

#### Study of the clinical efficacy of low-molecular-weight compounds tofacitinib for rheumatoid arthritis

Toyomitsu Tsuchida  
Institute of Rheumatic Disease, Tsuchida Clinic, Chiba, Japan

Conflict of interest: None

OBJECTIVE: Clinical effects of tofacitinib for RA is reported using ultrasonography. [Method] RMX bulking difficulty of the RA patients on our hospital 70-year-old, targeted biologics introduced difficult 46 cases, administration age average 78.6 years old. It was started in all cases tofacitinib 5mg 1T / day administered taking into account the age and renal function. And with time to enforce the ultrasound examination in the subject case, we compared the clinical results and ultrasound findings in retrospective. [Result] Among the administration 46 cases, stiffness of clinical symptoms, joint pain in 2 weeks administration, cases to improve had exceeded 80%. For over time 8 cases was able to perform an ultrasound examination of the cases more than administration after 6 months, those active synovitis was lost at ultrasonography was only one case. The remaining seven cases had residual activity of synovitis in all inspection

period. That also joint pain disappeared, synovitis is remained, it was those named just silent synovitis means quiet synovitis. [Conclusion] The clinical course of tofacitinib dosing in more than 70 years of age of older RA There are remarkable things but, in the ultrasonic inspection has residual activity of synovitis, as it was named exactly silent synovitis.

### P3-120

#### 20 leukocytapheresis (LCAP) cases with rheumatoid arthritis before biological DMARD (bDMARD) introduced; "LCAP First" therapy

Maki Kagitani<sup>1</sup>, Tohru Takeuchi<sup>2</sup>, Shigeki Makino<sup>2</sup>, Toshiaki Hanafusa<sup>3</sup>  
<sup>1</sup>Blood Purification Center, Osaka Medical College, <sup>2</sup>Clinical Immunology and Rheumatology, Osaka Medical College, <sup>3</sup>First Department of Internal Medicine, Osaka Medical College

Conflict of interest: None

[Objectives] bDMARD, its large amount of medical care, cause to give up introduction. In our hospital, "LCAP first" has been available as an alternative therapy since 2006. We report the results of 20 LCAP first cases. [Method] Medication, DAS28CRP are investigated at before LCAP start and at one month after the fifth, and checked having change or not. Furthermore, in 18 (a total of 21) examples which could be chased, disease activity and medication at October, 2014 are also investigated. [Result] Medication changeless is eight, adjustment of conventional DMARD (csDMARD) only is nine, bDMARD introduction were seven at one month after the fifth LCAP. DAS28CRP was decreased in all groups. At October, 2014, medication changeless is one, adjustment of csDMARD 7 (a total of eight), bDMARD introduction were a 10 (a total of 12), death caused by infection is one, hospital interruption 1 (a total of two). The remission case is two. In two cases, nausea and insufficient quantity of blood flow were observed as side effects. [Conclusion] LCAP can expect curative effect by a case. Furthermore, there is the case that can maintain only in csDMARD for a long term after LCAP, and the possibility that LCAP can contribute to RA medical treatment at the points of economically is suggested.

### P3-121

#### Efficacy of minocycline in the treatment of chlamydia antibody positive undifferentiated arthritis

Masanobu Ohishi, Yasuharu Nakashima, Ken Okazaki, Junichi Fukushi, Akiko Oyamada, Takuaki Yamamoto, Hidehiko Yuge, Yukihide Iwamoto  
Department of Orthopaedic Surgery, Kyushu University Hospital

Conflict of interest: None

[Objectives] Patients with seronegative arthritis (SNA) who were positive for either Chlamydia Trachomatis (ChT) or Chlamydia Pneumoniae (ChP) were diagnosed as Chlamydia antibody positive undifferentiated arthritis (ChUA). The current study aimed to evaluate the efficacy of minocycline (MINO) in those patients. [Methods] Among 16 ChUA patients, 14 patients were treated with MINO. The efficacy and side effects of MINO were investigated. Number and location of swollen and tender joints, presence of inflammatory back pain (IBP), sacroiliac pain (SI pain) and enthesitis and the value of C reactive protein (CRP) were also investigated. [Results] 15 cases were positive for ChP antibody and 6 cases were positive for ChT antibody. Among them, 5 cases were positive for both antibodies. No cases suffered IBP. One case complained SI pain. Number of swollen joints was 1.70 (0~6). Tender joints count was 2.55 (0~7). 12 cases were CRP-positive. In 9 cases out of 14 cases treated with MINO, swollen joints and tender joints were completely abrogated. 4 cases had to stop the medication due to side effects such as nausea and liver dysfunction. [Conclusion] ChUA is one of the differential diagnosis of SNA even without IBP, SI pain and enthesitis. MINO was efficacious in the treatment of ChUA.

### P3-122

#### Travel around Europe for the patients with collagen diseases and Its Effect

Katsuhiko Takabayashi  
Department of Medical Informatics, Chiba University Hospital, Chiba, Japan

Conflict of interest: None

[Objectives] To travel around Europe for the patients with collagen diseases who cannot go by themselves. [Method] We have been continuing tours to Europe for the collagen disease patients with a doctor and a nurse since 1993. [Result] More than 200 patients and their families participated without big trouble in 18 times. There are 65 patients who have experienced Europe; RA 20 SLE 17 PM/DM 4 Sjogren 4. They came mostly from Chiba prefecture but also from all parts of Japan. No patient was admitted to the hospital during and after the tour, though one patient slipped at the stairs of metro and went to a doctor. During and after the tour, none showed exacerbation of the disease. [Conclusion] Not only during the travel but after that, they are in good spirits even several months later and became active in their lives.

### P3-123

#### Treatment using Tramadol / acetaminophen combination tablets with biologic drugs for RA patients

Natsuko Nakagawa, Ken Takebe, Koji Tateishi, Yasuhiro Terashima, Miki Murata, Ryosuke Yoshihara, Yasushi Tanaka, Kazuko Shiozawa, Shigeaki Imura  
Kohnan Kakogawa Hospital, Rheumatic Center

Conflict of interest: None

[Objectives] Biologic agents have been changing dramatically the course of the treatment for rheumatoid arthritis (RA). In spite of the development of RA treatment, RA patients have been suffered from the joint pain. The purpose of this study is to evaluate the effectiveness of the treatment of RA patients with tramadol / acetaminophen combination tablets (TRAM/APAP). [Methods] Twenty-seven RA patients treated with TRAM/APAP and biologics were evaluated. They have been treated between Aug.1.2013 and Aug.31.2013. The mean age was 65 year-old. The mean doses of used TRAM/APAP were 2.6. [Results] At the time of follow-up, disease activity was suppressed by biologic agents. The patients' VAS decreased, although there were the differences among the patients. No serious side effects related were observed in patients received this treatment. [Conclusion] The effectiveness of TRAM/APAP for RA patients was reported. This therapy is thought to be useful for RA patients. This treatment will be considered as an option for RA treatment. The experiences and clinical information will be needed more in future.

### P3-124

#### Usefulness of Tramadol/acetaminophen combination tablets in pain management of patients with rheumatoid arthritis

Makoto Yaegaki  
Rokugo Orthopaedic Surgery and Rehabilitation Clinic, Aomori, Japan

Conflict of interest: None

[Objectives] I examined the usefulness of Tramadol / acetaminophen combination tablets (TRAM/APAP) for rheumatoid arthritis (RA) patients that they does not improve pain by performing anti-inflammatory therapy. [Methods] I subjected to the 11 cases using the TRAM/APAP combination tablet in RA patients between April to September in 2014. I studied the following items: age, observation period, complications, endpoint (symptom reduction or side effects.), RA score (DAS28-CRP, SDAI), and steroid (PSL) usage. Subject characteristics were as follows: gender: female 11 cases, man 0 case, average age: 68.5 years old (50-79), RA onset: 68.1 years (49-78). Physical characteristics are height 155.1 cm, weight 53.6kg, BMI 21.8. Used drugs were NSAIDs 6 cases, TRAM/APAP 11 cases, Sulphasalazine 5 cases, Bucillamine two cases, MTX 7 cases and steroid eight cases. [Results] SDAI was improved from 24.17 to 10.24 (p <0.05) and DAS28-CRP was improved from 4.03 to 2.82 (p <0.05). VAS was decreased from 67/100 to 23/100 (p <0.05). They showed both significant improvements. Also, usage of PSL was a significant reduction from 4.7mg/d to 2.7mg/d (p <0.01). [Conclusion] It has been suggested that TRAM/APAP was useful pain management at the time of introduction of MTX and in invalid cases of NSAIDs.

### P3-125

#### Human Trial of Liposomal Lactoferrin Supplementation for Rheumatoid Arthritis

Takaki Nojima<sup>1,2</sup>, Tetsu Oyama<sup>3</sup>, Ayuko Sogabe<sup>1</sup>, Hirofumi Watanabe<sup>1</sup>, Kazuhiko Kumagai<sup>1</sup>, Satoshi Yamasaki<sup>1</sup>, Eiji Sugiyama<sup>1</sup>

<sup>1</sup>Department of Clinical Immunology and Rheumatology, Hiroshima University Hospital, <sup>2</sup>Nojima Internal Medicine Clinic, <sup>3</sup>Oyama Clinic

Conflict of interest: Yes

[Purpose] It is known that lactoferrin (LF) inhibits hepatitis C virus viremia, intestinal polyp growth and inflammation of chronic periodontitis. And, oral pretreatment of liposomal LF (LLF) exhibited suppressive effects on CCl<sub>4</sub>-induced hepatic injury in rats. The aim of this study is to determine whether oral LLF can influence to the clinical information in rheumatoid arthritis (RA). [Method] Data and clinical information on 20 patients with RA were collected at the beginning of the trial and at 1, 2, 3 months. Patients took six tablets orally everyday for 3 months. One tablet contained LLF at 45mg. [Result] The average of DAS28 (CRP) was decreased gradually (3.21→2.85→2.83→2.68). EULAR response was good response: one, moderate response: seven and no response: twelve. C reactive protein (mg/dL) slightly reduced (0.86→0.71→0.72→0.60). mHAQ was not improved (0.48→0.52→0.50→0.55). Rheumatoid Factor, Anti-CCP antibody and MMP-3 were no changes by the comparison at the beginning of the trial and at 3 months (234→224 IU/ml, 287→271 U/ml, 128→136 ng/ml). Adverse events: 3 patients with loose passage and one patient with labial herpes. [Discussion] Our data suggested that there were benign improvement of RA clinical information in some RA patients with oral administration of LLF.

### P3-126

#### A juvenile case of calcium pyrophosphate crystal-induced chronic arthritis effectively treated with TNF blocker, adalimumab

Kazutaka Ouchi<sup>1</sup>, Shinji Akioka<sup>1</sup>, Norio Nakagawa<sup>1</sup>, Ryo Oda<sup>2</sup>, Satoru Nakamura<sup>2</sup>, Toshikazu Kubo<sup>2</sup>

<sup>1</sup>Department of Pediatrics, Post Graduate of Medical Science, Kyoto Prefectural University of Medicine, <sup>2</sup>Department of Orthopaedics, Post Graduate of Medical Science, Kyoto Prefectural University of Medicine

Conflict of interest: None

Calcium pyrophosphate (CPP) deposition, commonly observed in elderly people, does not only induce pseudogout but chronic polyarthritis. The management is mostly focused on symptomatic control for attacks, but in case of chronic arthritis frequent glucocorticoids (GC) administrations are compelled for achieving remission. We report a juvenile patient with CPP crystal-induced chronic arthritis resistant to conventional medications, who was successfully treated with adalimumab. A 14-year-old male was referred to our clinics due to polyarthralgia with evidence of CPP crystal in joint fluid. His diagnosis was CPP crystal-induced chronic polyarthritis with synovitis, enthesitis and crystal depositions in hyaline cartilage. NSAID, colchicine or methotrexate was not effective. Intra-articular GC injection was only limitedly available. As an intractable case, he was medicated with adalimumab, which brought dramatic improvement of joint pain and amelioration in clinical findings. With recent advances of innate immunity in understanding inflammation, CPP crystal-induced arthritis could be considered as a result of excess IL-1 signaling. Beside IL-1 blocking, TNF blockade might be a potent strategy in management of intractable cases with crystal arthritis as well as other rheumatic disorders.

### P3-127

#### Bone histomorphometric findings of ankylosing spondylitis; a case report

Naoki Kondo, Junichi Fujisawa, Naoto Endo

Division of Orthopaedic Surgery, Department of Regenerative and Transplant Medicine, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Conflict of interest: None

[Case] Thirty six years old male was diagnosed as ankylosing spon-

dylitis. HLA-B27 was positive. His chief complaint was front gaze disorder. He received surgery of wedge corrected osteotomy of the third vertebral body. Iliac bone graft was also performed. A part of iliac bone was subjected to histological examination after informed consent. It was processed to bone histomorphometric analysis. Each bone volume parameter was low compared to that of age-gender matched control (bone volume=8.92%, trabecular thickness=81.50, and wall thickness=26.78). Each osteoid parameter was also low (osteoid volume=3.37, osteoid surface=7.83, and osteoid thickness=4.87). Especially, osteoblast surface was extremely low (1.81). Each bone resorption parameter was low (eroded surface=1.6%, osteoclast surface=0.27%). These findings showed low bone turnover. Furthermore, cortical bone demonstrated thinning and porosity, suggesting that bone intensity was decreased. Bone specific alkaline phosphatase was normal (17 U/l). TRACP-5b was slightly low (136 mU/dl). Urine NTx was elevated (368.1). The data of bone resorption markers were diverse. Serum 25OH-D was deficient (16 ng/mL). [Clinical significance] The report is noteworthy for demonstrating the condition of bone dynamics in ankylosing spondylitis.

### P3-128

#### The clinical outcome of Total Shoulder Arthroplasty

Tetsuro Ushio, Hisaaki Miyahara, Yukio Esaki, Goh Hirata, Satoshi Kamura, Koji Sakuraba

Kyusyu Medical Center, Fukuoka, Japan

Conflict of interest: None

[Objectives] We perform Total Shoulder Arthroplasty (TSA) or Hemiarthroplasty on patients with pain and deformity caused by Rheumatoid arthritis (RA). The purpose of this study is to evaluate the clinical outcome after TSA in patients with RA. [Methods] From 2007, 11 patients with RA were performed TSA. All of them were female, and the average age at the time of surgery was 65.8 years old (ranged 48-84). Physio-Shoulder System was used in 5 cases and B/F Shoulder in 6 cases. The Patients follow-up averaged 32.5 months (minimal 3 months). All patients were evaluated before and after surgery with range of motion, JOA score, joint deformity, presence of cuff tear, control of RA, intraoperative findings, and complications. [Results] There were statistically significant improvements in elevation (71.82 degrees to 136.4 degrees), and JOA score (38.36 to 83.55). The patients with intact cuff tended to be high in JOA score, but the elevation angle in 2 patients with cuff tear were unfortunately 70 degrees and 90 degrees. There were radiolucent zone around the glenoid component in 6 cases. The case with cuff tear and bad control of RA suffered from loosening of glenoid component, but the other 5 cases didn't. [Conclusion] The presence of cuff is very important for the outcome of TSA.

### P3-129

#### Short term result of Discovery elbow arthroplasty

Yasunori Omata, Yuho Kadono, Tetsuro Yasui, Naoko Shoda, Jinju Nishino, Sakae Tanaka

Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo

Conflict of interest: None

We investigated short term result of semi-constrained total elbow arthroplasty using Discovery elbow system. 13 cases (13 elbows) were analyzed whether there is loosening of the implant or a radiolucent line. Three cases had loosening of the implants and four cases had radiolucent lines. There is a tendency that the loosening and radiolucent line exist in humeral implant or in revision cases.

### P3-130

#### Primary total elbow replacement for elbow fractures in the patients with rheumatoid arthritis

Kenji Onuma<sup>1</sup>, Mamoru Fujita<sup>3</sup>, Katsufumi Uchiyama<sup>1</sup>, Naonobu Takahira<sup>2</sup>, Masashi Takaso<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Kitasato University School of Medicine, <sup>2</sup>Department of Rehabilitation, Kitasato University School of Allied Health Science, <sup>3</sup>Department of Orthopaedic Surgery, Toyohashi Municipi-

pal Hospital

Conflict of interest: None

[Objectives] Open reduction and internal fixation of elbow fractures often do not provide satisfactory results in rheumatoid patients. Previous studies reported satisfactory results of total elbow arthroplasty for the patients with rheumatoid arthritis. The aim of this study was to retrospectively survey rheumatoid patients with elbow fracture who undergo total elbow arthroplasty in our hospital. [Methods] From 2001 to 2011 a total elbow arthroplasty (Coonrad-Morrey type) was performed on 4 patients (average age 53.5 years) who presented with 3 distal humeral fractures and an olecranon fracture. The mean time of follow-up with clinical and radiological assessment was 6 years and 4 months. [Results] The Mayo score showed a good functional result with an average of 90 points. The average range of motion (flexion/ extension) of all patients was 143/-43.8 degrees. Pseudoarthrosis of medial condyle was found by X-ray examination in 1 case, asymptomatic radiolucent line in 1 case. Rupture of distal triceps was found in 1 case after 10 weeks of the operation and performed reconstruction surgery using palmaris longus autograft. [Conclusion] Primary total elbow arthroplasty for elbow fractures in rheumatoid patients has good functional results and is an alternative to osteosynthesis.

### P3-131

#### **Surgical approach with semi- constrained TEA for severe destructive RA arthropathy**

Hirota Iura, Koji Sakuraba, Yukio Esaki, Goh Hirata, Satoshi Kamura, Masanari Ota, Hisaaki Miyahara

Department of Orthopedics and Rheumatology, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

Conflict of interest: None

Total elbow arthroplasty (TEA) is a good method to treat joint failures, such as pain, joint instability and motion limitation caused by rheumatoid arthritis (RA). There are two devices in the TEA system, semi-constrained type and non-constrained type, and the indication and performance of them were some reported previously. However, the research for treatment of severe destructive arthropathy with high level instability was very few in number. So we reported two case experiences which were performed semi- constrained TEA for severe destructive RA arthropathy. The case were 70 and 74 years women, disease durations were 48 and 17 years. X-ray assessment were both Larsen V. Periods under observation were 4 years and 6 months. Before surgery, elbow flexion was 110 degree or 120 degree, and which extension was -70 degree or -80 degree. We could not point out loosening and radiolucent areas at the final visit, together. One of two case underwent open reduction and internal fixation, because of suffering olecranon fracture 3years after surgery. Therefore, semi-constrained TEA was a good procedure for treatment of RA elbow arthropathy with severe destruction in short duration, because of improvement in elbow function, stability and pain.

### P3-132

#### **Insufficiency fracture of the radius after Sauve-Kapandji procedure in a rheumatoid arthritis patient**

Mineyuki Zukawa<sup>1</sup>, Ryusuke Osada<sup>1</sup>, Hiraku Motomura<sup>1</sup>, Isao Matsushita<sup>1</sup>, Hirofumi Taki<sup>2</sup>, Tomoatsu Kimura<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, University of Toyama, Toyama, Japan, <sup>2</sup>Department of Internal Medicine, University of Toyama, Toyama, Japan

Conflict of interest: None

[Case] A 63-year old woman had been diagnosed with rheumatoid arthritis (RA) at the age of 37 years and was treated with methotrexate and etanercept. She had undergone Sauve-Kapandji (S-K) procedure of the right wrist combined with tendon graft, due to tendon rupture. Although she had not experienced any recent trauma, right forearm pain and swelling increased 4 months after the operation. Radiographs showed a fracture of the radius at the level of the excision osteotomy of the distal ulna. Her bone density was 61% of the young adult mean (YAM). We immobilized her forearm in a long arm cast and medicated teriparatide. The frac-

ture had healed after 5 months. She acquired full supination and pronation because after the S-K procedure in spite of angulation deformity. [Discussion] Incidence of radius fracture after S-K procedure is only 1/87 in our RA patients. It is several rare fractures. We considered this factor were repeated load and rotation force without ulnar support, osteoporotic bone, and high activity of daily life under the biological agent use. Only 2 cases of this fracture were reported recently. Although they were performed plate fixation for fracture, our case was healed by conservative therapy with teriparatide.

### P3-133

#### **Three cases of total joint arthrodesis for severely destructed RA wrists**

Chisa Okura<sup>1</sup>, Yukio Yonemoto<sup>1</sup>, Koichi Okamura<sup>1</sup>, Takahito Suto<sup>1</sup>, Asami Abe<sup>2</sup>, Kenji Takagishi<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine, Japan, <sup>2</sup>Department of Rheumatology, Niigata Rheumatic Center, Japan

Conflict of interest: None

[Objectives] The wrist is an important joint in order to exhibit the hand function. In RA, patients with pain and instability are greatly failure gripping function. Here we show for the RA hand joints showed a highly destruction in RA joints, We experienced the three cases who underwent hand total joint arthrodesis. [Case 1]64-year-old woman, had developed RA when 48-year-old, she gave the extension failure of the right ring finger and little finger. Because carpal had dislocated the palmar side and deformation of Larsen grade V, we underwent a right total joint arthrodesis and tendon transfer using a Wrist Fusion Rod (WFR). [Case 2]72-year-old man, had developed RA when 47-year-old. Because the swelling of the left wrist joint lasts from a few months ago and the deformation of the joint has progressed, we selected the total joint arthrodesis of left wrist by WFR. [Case 3]69-year-old woman, developed RA when 28-year-old. Her right wrist and right thumb have mutilans deformation, there is a failure of the gripping function and pinch function for instability. We underwent the total joint arthrodesis of right wrist by WFR and arthrodesis of IP joint and Swanson implant arthroplasty of MP joint of the right thumb.

### P3-134

#### **Rradiographic analysis of the wrists with Rheumatoid arthritis underwent distal radioulnar joint arthroplasty**

Satoshi Kamura<sup>1</sup>, Yukio Esaki<sup>1</sup>, Goh Hirata<sup>1</sup>, Koji Sakuraba<sup>1</sup>, Kenjiro Fujimura<sup>3</sup>, Hirota Iura<sup>1</sup>, Masanari Ota<sup>1</sup>, Tetsuro Ushio<sup>4</sup>, Hisaaki Miyahara<sup>1</sup>

<sup>1</sup>Department of Orthopaedics and Rheumatology, National Hospital Organization, Kyushu Medical Center, <sup>2</sup>Mitsuyasu Orthopaedic Hospital, <sup>3</sup>Department of Orthopaedics, Hamanomachi Hospital, <sup>4</sup>Department of Orthopaedics, Kokura Memorial Hospital

Conflict of interest: None

[Objectives] We usually perform the Sauve-Kapandji (S-K) procedure for disorders of the distal radioulnar joint of rheumatoid arthritis (RA). However, for patients with poor bone quality, S-K procedure is difficult to preserve the radioulnar diameter of the wrist, which may result in post-operative ulnar shift of the carpus and pain. The purpose of this study was to review the radiographic changes of RA patients who underwent a S-K procedure. [Methods] S-K procedure was performed in 21wrists of 19 RA patients between 2003 and 2012. The radiographic evaluation included a measurement of the ulnar translation of the carpus, the distal radioulnar width and the distance between proximal and distal ulnar stump. [Results] The ulnar translation of patients with bony fusion of the carpus was tend to be smaller compared to carpus restored joint space. Although there was little change about the distal radioulnar width, some patients showed that distal ulnar stump failed to maintain the radioulnar width. [Conclusion] The S-K procedure is now an established treatment option for disorders of the distal radioulnar joint of RA. Our results suggested that the statement of carpal bone fusion might be important factor for deciding surgical procedure for RA wrist.

### P3-135

#### MP joint arthroplasty with silicon implant for ulnar drift deformity in rheumatoid arthritis

Seiichi Kawamura

Department of Orthopaedic Surgery, Oita Red Cross Hospital, Oita, Japan

Conflict of interest: None

[Objectives] The ulnar drift deformity of fingers is relevant to activities of daily living (ADL). The purpose of this study was to estimate the effect of the arthroplasty with silicon implant. We reviewed 12 cases, 16 hands (49 joints) who had taken arthroplastic surgery with silicon implant. [Methods] We assessed the following findings: the arc of motion in the mp joint, the patient's satisfaction and the radiographic change after surgery. The average duration of follow-up was 58.1 months (12 - 140 months). [Results] The arc of motion was improved from an average of 15 degrees to an average of 47 degrees. The improvement enabled the patients to hold a bottle and scoop up water with their hands. Therefore the patients showed general satisfaction about the surgical outcome. [Conclusion] Arthroplasty with silicon implant is effective for ulnar drift deformity in rheumatoid arthritis.

### P3-136

#### Clinical Results of total hip arthroplasty for patients with rheumatoid arthritis

Kaneaki Tawada, Kunio Yamada, Hideki Muro, Keisuke Hoshino, Shinji Funahashi, Makoto Fukuta, Hidetoshi Iwata

Department of Orthopaedic Surgery, Komaki City Hospital

Conflict of interest: None

[Objectives] Total hip arthroplasty (THA) is an effective treatment option for patients with rheumatoid arthritis (RA). The purpose of this study was to investigate the clinical results of THA for rheumatoid patients in our department. [Methods] Fifty-nine THAs in 49 patients performed between 2004 and 2013 at our department were included in this study (18 males, 31 females, average age 66.9 years old). Implant fixation was achieved with all cemented in 1 joint, stem cemented in 5 joints and uncemented in 53 joints. The patients background, clinical course, JOA score and complications were investigated. [Results] During the follow up period, 9 patients died. Finally, 47 hips in 38 patients were investigated. Average follow up period was 5.7 years. Average JOA score improved from 49.3 points preoperatively to 82.0 points at the final follow up. Complications included intraoperative proximal femoral fracture in two cases, pseudotumor in two cases and dislocation in two cases postoperatively. [Conclusion] There have been reports on higher complication rate after THA for RA compared to OA. We observed no infection and 3 dislocations in this study. Careful observation is needed for rheumatoid patients who underwent THAs.

### P3-137

#### The Clinical Results of THA for RA Patients

Natsuo Konishi<sup>1</sup>, Keiji Kamo<sup>2</sup>, Seiya Miyamoto<sup>3</sup>, Yusuke Sugimura<sup>4</sup>, Yoichi Shimada<sup>5</sup>, Naohisa Miyakoshi<sup>5</sup>

<sup>1</sup>Dept. of Orthop. Surgery, Akita Kousei Medical Center, Akita, Japan,

<sup>2</sup>Dept. of Orthop. Surgery, Akita Rosai Hospital, Akita, Japan, <sup>3</sup>Dept. of

Orthop. Surgery, Nakadori General Hospital, Akita, Japan, <sup>4</sup>South Akita

Orthopedic Clinic, Akita, Japan, <sup>5</sup>Dept. of Orthop. Surgery, Akita University

Graduate School of Medicine, Akita, Japan

Conflict of interest: None

[Objectives] We report about the clinical results of THA for RA patient in 16 years from December in 1997 to July in 2014. [Methods] Total operations were 300 cases. Primary operations (P group) were 263 cases, and 37 cases were revision operations (R group). 27 cases (9.0%) were the RA patients, 22 cases were in the P group (8.4%), 5 cases were in the R group (13.5%). Average time of disease duration was 9.8 months. The average age was 63.2 years old at the time of surgery. Average of preoperative JOA score was 49.7 points. We used mainly PSL cup / SecurFit series by Stryker Corporation in the P group. In the R group we replaced 5 implants of 4 cups and 1 stem. [Results] Average of JOA score was

80.2 points after surgery. In the P group no one was performed revision operation. In the R group we had to operate three times in the same patient. Finally his third operation was successful. [Conclusion] In THA operation for RA patients, we have some technical problems; for example, central migration, poor bone quality, and compromised condition, multiple joint deformations and dysfunctions. It is important that we have preoperative preparation in cases of advanced deformation and bone defect. Including the control of RA, careful follow-up after surgery is desirable as RA patients.

### P3-138

#### Direct Anterior Approach for Hip Arthroplasty: Surgical Complications

Hiromasa Kanno

Department of Orthopedic Surgery, Jusendo General Hospital, Koriyama, Japan

Conflict of interest: None

[Objectives] The direct anterior approach (DAA) is well-established as minimal invasive technique in elective orthopedic hip surgery. However, its complications are not well defined in the literature. Our study emphasizes the complications of total hip arthroplasty (THA) and bipolar hip hemiarthroplasty (BHH) using DAA. [Materials] We performed BHH in 19 cases and THA in 28 cases from June 2011 to April 2013, using DAA. [Results and Discussion] 1. One rasp perforation occurred during surgery. During the femoral procedure, the leg was adducted and externally rotated. The rasp therefore tended to move medially and perforate posteriorly. 2. Three of the 28 cases (10.7%) experienced femoral nerve palsy during the THA procedure. The three patients gradually improved and made a complete recovery at 3 to 12 months. The direction of the retractor could have been wrong. There is a possibility that the rectus femoris muscle was strongly retracted near the femoral nerve. 3. One intraoperative fracture of the proximal femur around femoral prosthesis occurred. Thus we performed fracture fixation by cerclage wiring. [Conclusion] Three of 28 cases (10.7%) experienced femoral nerve palsy during THA using DAA. We should care about femoral nerve palsy in THA using DAA.

### P3-139

#### Time course analysis of outcomes after total hip arthroplasty in hemodialysis patients

Yasumasa Ito

Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan

Conflict of interest: None

[Objectives] We retrospectively evaluated the time course after total hip arthroplasty (THA) to clarify its usefulness in hemodialysis (HD) patients. [Methods] We examined 8 patients (8 hips) who underwent THA with PerFix system. They were followed up for a minimum of 2 years. The average age at THA was 57 years. The average duration of HD before THA was 8.5 years. Clinical outcomes were evaluated preoperatively, at 1 year postoperatively and at the final follow-up of 8.0 years on average postoperatively by JOA score, D'Aubigne & Postel score and Oxford score. [Results] Four out of 8 patients died during the follow up period. No revision was required. The average JOA, D'Aubigne & Postel and Oxford scores were significantly improved from 41, 8.4 and 14 preoperatively to 82, 15.5 and 38 at 1 year postoperatively, respectively. Although these scores declined to 75, 14.6 and 35 at the final follow-up, respectively, the significant improvement in the scores was maintained at the final follow-up. [Conclusion] THA significantly improved hip functions at 1 year postoperatively. Although this improvement seems to gradually decline over time, improved hip functions continue over 2 years postoperatively. Despite HD-related problems, THA can improve short and mid-term postoperative outcomes.

### P3-140

#### A fracture of femur with implants like the atypical femoral fracture: a case report

Masanari Ota, Koji Sakuraba, Yukio Esaki, Goh Hirata, Satoshi Kamura,



Hirotaaka Iura, Hisaaki Miyahara  
Orthopaedics Surgery and Rheumatology, Clinical Research Center, Kyusyu Medical Center, Fukuoka, Japan

Conflict of interest: None

In the task force of American Society for Bone and Mineral Research, the fracture of femur with implants is excluded from the atypical fracture. We report a case of the fracture of femur with implant like the atypical femoral fracture. The case was a 60-year-old woman who had been suffered from rheumatoid arthritis. She had taken minodronate for two years to treat osteoporosis. Having a total hip arthroplasty in her left hip at the age of 38, she had a mass in the left inguinal region. Because the mass was growing bigger and bigger, she had a medical examination in our hospital. X-ray showed loosening of the shell. And iliopsoas bursitis was suspected from CT. Thus reimplantation was planned. At that time, X-ray showed local bone thickness of the lateral femoral shaft. Thereafter, she had a left femoral pain and could not stand up when she went down the stairs, and was taken to our hospital. X-ray showed a fracture at the distal end of the implant stem. We performed osteosynthesis with LCP-locking compression plate and started medication of teriparatide and low intensity pulsed ultra-sound. Left femoral fracture achieved bone union smoothly without delayed healing. It is suggested that there is a fracture of femur with implant like the atypical femoral fracture.

### P3-141

#### Transtrochanteric/intertrochanteric osteotomy for steroid-induced osteonecrosis of the femoral head

Shunji Nakano<sup>1</sup>, Yoshiaki Minato<sup>2</sup>, Katsuhiro Kinoshita<sup>2</sup>, Masahiko Azuma<sup>2</sup>, Koichi Sairyō<sup>3</sup>

<sup>1</sup>Department of Orthopedic Surgery, Tokushima Municipal Hospital, Tokushima, Japan, <sup>2</sup>Department of Internal Medicine, Tokushima Municipal Hospital, Tokushima, Japan, <sup>3</sup>Department of Orthopedics, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan

Conflict of interest: None

[Objectives] We report 3 patients who had undergone transtrochanteric/intertrochanteric osteotomy for steroid-induced osteonecrosis of the femoral head. [Patients and Results] Case 1: A 30-year-old woman with systemic lupus erythematosus was treated with steroid pulse therapy. We performed right and left transtrochanteric rotational osteotomies in 2008 and 2011, respectively. However, both femoral heads were destroyed. We converted to right and left total hip replacements in 2012 and 2013, respectively. Disease control with <10 mg of steroid was difficult. Case 2: A 30-year-old man with nephrotic syndrome was treated with steroid pulse therapy. He had right transtrochanteric rotational osteotomy in 2009. He had disease remission in 2010, and his hip condition was good. Case 3: A 52-year-old man with aortic syndrome was treated with steroid pulse therapy. We performed left intertrochanteric curved varus osteotomy. His disease state was stable with 5 mg of steroid, and his hip condition was good. [Conclusion] Transtrochanteric/intertrochanteric osteotomy for osteonecrosis of the femoral head is an acceptable procedure for relieving pain if disease control can be achieved with ≤5 mg of steroid.

### P3-142

#### Rheumatoid arthritis of destructive hip arthropathy complicated with huge trochanteric bursitis; A case report

Naoki Kondo<sup>1</sup>, Junichi Fujisawa<sup>1</sup>, Katsumitsu Arai<sup>2</sup>, Naoto Endo<sup>1</sup>

<sup>1</sup>Division of Orthopaedic Surgery, Regenerative and Transplant Medicine of Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, <sup>2</sup>Division of Orthopaedic Surgery, Niigata Prefectural Chuo Hospital, Joetsu, Japan

Conflict of interest: None

[Case] Forty three year old female was diagnosed as RA 8 years ago. Ten mg/day of prednisolone was treated due to her pregnancy and 4mg/week of methotrexate (MTX) was started after delivery. MTX was loaded up to 8mg/week and then 50mg/week of etanercept (ETN) was introduced. Four years ago, she complained of a subcutaneous mass in her

right buttock without pain. MRI showed large mass (4.5 x 7.5 x 12 cm) was detected around greater trochanter and beneath gluteus maximus. Puncture analysis showed yellowish and clear fluid. Bacterial and mycobacterial culture showed negative and no malignancy was demonstrated. She was diagnosed as trochanteric bursitis. A year ago, she complained of her right hip pain and could not walk. X-ray findings showed destructive change within 6 months. Right total hip arthroplasty was performed. Intraoperative findings showed the communication between trochanteric bursa and hip joint. Seven months after the surgery, she could walk without support. [Discussion] The existence of the communication between trochanteric bursa and hip joint possibly caused destructive hip arthropathy. [Clinical significance] Some reports of iliopsoas bursitis complicated with hip joint destruction in RA cases were found. Our case, trochanteric bursitis, is exclusively rare.

### P3-143

#### Arthroscopic surgery of the ankle for RA patients under anti-TNF therapy

Yukio Shigeyama, Masanori Hamada, Yuji Moriya  
Department of Orthopaedic Surgery, Kibikogen Rehabilitation Center

Conflict of interest: None

[Objectives] Arthroscopic surgery is less invasive and more useful for RA patients under anti-TNF therapy. We present a report of two patients with RA, who had taken an anti-TNF blockade and needed an ankle arthroscopic surgery for the RA ankle. [Methods] One is a 56-aged female RA patient with 7-year RA history. After discontinuation of the 3-year infliximab therapy, her gait was impaired due to swelling and pain of the right ankle. As magnetic resonance image revealed synovitis of the ankle, arthroscopic synovectomy was performed in order to regain the function and prevent progress of the destruction. The other is a 68-aged female with 15-year RA history. Even in remission after 6-year infliximab therapy, the right ankle pain brought gait impairment. As X-ray showed Larsen grade 4 without retention of the joint space, arthroscopic arthrodesis was performed in order to recover walking ability. [Results] After arthroscopic synovectomy, the ankle function was regained. Furthermore, arthroscopic arthrodesis resulted in both bony union and gait without crutches in three months. [Conclusion] Arthroscopic surgery of the ankle might be useful for RA patient even under anti-TNF therapy, because arthroscopic surgery is less invasive as well as promising.

### P3-144

#### Soy isoflavone supplementation may be beneficial to cartilage metabolism in ovariectomized rats

Yuko Sugioka<sup>1</sup>, Toshiya Toda<sup>2</sup>, Tatsuya Koike<sup>1,3</sup>

<sup>1</sup>Center for Senile Degenerative Disorders (CSDD), Osaka City University Medical School, Osaka, Japan, <sup>2</sup>Fujicco Corporation Limited, Research and Development Department, <sup>3</sup>Search Institute for Bone and Arthritis Disease (SINBAD), Shirahama Foundation for Health and Welfare

Conflict of interest: Yes

[Objective] Estrogens have been implicated in articular cartilage metabolism and the pathogenesis of postmenopausal osteoarthritis. Isoflavone is classified as both phytoestrogens and selective estrogen receptor modulators. The phytoestrogenic effects of isoflavone might have some effect for postmenopausal osteoarthritis. This study evaluated the effects of the soy isoflavone on cartilage metabolism in ovariectomized (OVX) rats. [Method] Six-month-old female rats were divided into three groups: a sham-operated (sham) group on a regular diet, OVX group on a soy isoflavone diet (OVX iso) [50µg/g/day] and a regular diet (OVX cont). Rats were sacrificed at 9 weeks after operation. Knee joints were removed and stained with toluidine blue. Cartilage destruction was scored on a scale from 0 to 3, ranging from fully stained cartilage (score 0) to distained more than half cartilage (score 3). [Result] OVX rats showed a significantly higher body weight than sham rats at week 9 ( $p < 0.05$ ). The damage score for cartilage was significantly higher in OVX cont (1.27) than in sham (0.19,  $p < 0.001$ ). Scores in OVX iso (0.71) was higher than in sham ( $p = 0.016$ ), but lower than in OVX cont ( $p = 0.016$ ). [Conclusion] Our data suggest that the soy isoflavone diet may be beneficial to postmenopausal osteoarthritis.

### P3-145

#### The bones are a key player for the pathophysiology of hip osteoarthritis and its joint pain

Yukio Nakamura<sup>1</sup>, Hiroyuki Kato<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Shinshu University School of Medicine, <sup>2</sup>Kamimura Clinic

Conflict of interest: None

**[Objectives]** The aim of this study was to investigate whether bone alterations detected by hip MRI were associated with subsequent primary hip OA with accompanying joint pain. **[Methods]** We enrolled 19 hip OA patients regardless of the KL scale. They were followed up using MRI examination, plain radiograph. We classified them into the following 2 groups. Group A: the patients whose pain was improved by treatment, Group B: the patients whose pain still continued. **[Results]** In Group A, joint pain in all 10 cases disappeared or was much improved. Radiographic OA progression occurred in 7 of 8 cases. Bone signal changes detected by MRI in 6 of 7 cases disappeared. In Group B, treatment was continuously performed because of the remaining joint pain in all 9 cases. Radiographic OA progression occurred in 8 of 9 cases. Bone signal alterations were remained in all patients by MRI. The age in Group B was significantly higher than that of Group A **[Conclusion]** This study showed the following in most patients: 1) hip OA with joint pain had bone alterations detected by MRI, 2) the bone alterations disappeared when joint pain was improved. These findings indicate that the pathophysiology of OA, joint pain, and the progression of OA may be due to primarily bone affection.

### P3-146

#### The role of paired-immunoglobulin-like type 2 receptor alpha (PILR $\alpha$ ) and CD99 on human osteoclastogenesis

Toru Yago, Yuki Nanke, Manabu Kawamoto, Tsuyoshi Kobashigawa, Hisashi Yamanaka, Shigeru Kotake

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: None

**[Background]** PILR $\alpha$  is one of the IgG superfamily and it contains ITIM motifs at intracellular. CD99 is one of the ligands for PILR $\alpha$ . It has been reported that anti-PILR $\alpha$  antibody (Ab) reduces inflammation in arthritis models in mouse (Sun Y. 2014). **[Objective]** To investigate the effect of PILR $\alpha$  and CD99 on human Oc-genesis. **[Method]** 1) PILR $\alpha$  expression on monocytes (Mo) for RA patients or healthy controls by FCM. 2) The expression of PILR $\alpha$  or CD99 in human Oc was analyzed by RT-PCR or immunohistochemical staining (IHC). 3) Human Mo were cultured with M-CSF for 3 days. Next, Mo were cultured with M-CSF and sRANKL. We simultaneously added anti-PILR $\alpha$  or anti-CD99 Ab. After 10 days, Oc formation was evaluated by IHC for anti-CD51/61 Ab. **[Results]** PILR $\alpha$  protein was expressed on human Mo. The MFI of PILR $\alpha$  tended to be higher in RA patients compared to healthy controls. The mRNA expression of PILR $\alpha$  and CD99 was detected in human Oc. The expression of PILR $\alpha$  by IHC was decreased as Mo differentiated to Oc. Anti-PILR $\alpha$  Ab and anti-CD99 Ab dose-dependently inhibited human Oc-genesis. **[Conclusion]** We demonstrated that the interaction of PILR $\alpha$  with CD99 is associated with human Oc-genesis. Both PILR $\alpha$  and CD99 could be therapeutic targets for bone destruction in RA.

### P3-147

#### Bone Metabolism before and after Total Knee Arthroplasty

Kazushi Haraguchi

Department of Orthopaedic Surgery Japan Seafarers Relief Association Moji Ekisaikai Hospital, Kitakyushu, Japan

Conflict of interest: None

**[Objectives]** Bone metabolism before and after TKA is affected by subchondral bone marrow lesion, bone remodeling after operation, change of activity. **[Methods]** Among 60 patents received TKA (exclude bisphosphonate dosage cases), postoperative values of YAM% of lumbar spine and femoral neck, makers of bone turn over (TRACP-5b, P1NP)

were compared with preoperative values. **[Results]** Preoperative YAM% was lumbar spine 93.2 $\pm$ 23.1, femoral neck 74.5 $\pm$ 16.4%. TRACP-5b was 443.5 $\pm$ 219.6 mU/dL and P1NP was 52.2 $\pm$ 36.9 $\mu$ g/L. After TKA less than seven months (n=51), 8-10 months (n=7), 11-13 months (n=18), 14 months later (n=22), a mean rate of changes (100-postoperative value / preoperative value %) were lumbar spine YAM% (-0.7, 0.7, 2.4, 3.6), femoral neck YAM% (-1.4, 0, 0.6, 0.7), TRACP-5 (17.9, 5.9, -15, -6.3), and P1NP (45.4, -14.6, -6.9, -20.2). BMD decreased slightness after TKA in six months, but is increased afterwards. Makers showed sthenia of bone turn over, predominance of bone formation in six months and it decreased below in preoperation. **[Conclusion]** It was guessed that bone hypermetabolism before TKA occurred because of the bone marrow lesion, postoperative bone formation sthenia was caused by the bone remodeling after operation, and postoperative increase in BMD was a result of activity increase.

### P3-148

#### Total knee arthroplasty for the patients with psychiatric diseases

Atsushi Yokota

Department of Orthopaedic Surgery, Aino Hospital

Conflict of interest: None

**[Objectives]** Total knee arthroplasty (TKA) for the patients with psychiatric disease (PD) is considered to be relative contraindication. We have performed TKA for those patients who have severe pain and disability of daily living. **[Results]** Case 1: a 66 year-old male who had schizophrenia has suffered from gait disturbance over 2 years. He underwent PS type TKA. Immediately after surgery, he wandered around the ward due to postoperative delirium, but afterward successfully recovered. Case 2: a 63 year-old female who had depression and diabetes mellitus (DM) could not continue therapeutic exercise due to knee pain, which resulted in deterioration in obesity and DM status. The PS type TKA was performed. She fell down 2 weeks after surgery. The X-ray showed lateral subluxation of the patella. Revision surgery was performed. Case 3: a 57 year-old female who had schizophrenia and RA fell down and had fracture of lateral tibial plateau. She dropped out the initial cast fixation since her mental status deteriorated, which resulted in painful knee joint with valgus deformity. She underwent semi-constrained TKA. Postoperatively she fell down and had the operation-wound maceration. **[Conclusion]** TKA for the patient with PD needs careful management in order to avoid perioperative complications.

### P3-149

#### Conservative treatment with teriparatide is effective for periprosthetic fracture accompanying slight transposition

Hiroshi Yonezu, Hiroshi Mikami

Department of Orthopaedic Surgery, Oe Kyodo Hospital, Tokushima, Japan

Conflict of interest: None

**[Introduction]** The incidence of periprosthetic fracture after femoral head replacement has recently increased with increases in the number of operative cases and the aging of the population. We report our experience with one case of periprosthetic fracture treated with teriparatide. **[Case]** Patient was 85-year-old, woman who underwent femoral head replacement for a femoral neck fracture 6 months prior. She presented our hospital after incurring an injury due to a fall. On radiography, a periprosthetic fracture (type B1 in the Vancouver classification system) with slight transposition was observed in the trochanter area. The bone density was 66% and 68% of the YAM at the lumbar vertebral and proximal femoral levels, respectively. Because the transposition was slight, we chose to perform conservative treatment. In addition, we started weekly injections of teriparatide after hospitalization. We confirmed callus formation on CT performed at 3 weeks after injury, at which time she started full-weight-bearing walking. She was discharged from the hospital at 4 weeks after the injury. **[Conclusion]** We conclude that conservative treatment with teriparatide is effective for periprosthetic fracture accompanying slight transposition.

### P3-150

#### **Possible trimethoprim-sulfamethoxazole induced aseptic meningitis in systemic lupus erythematosus**

Toshiki Kido, Hiroyuki Honoki, Satoshi Yamaguchi, Maiko Obi, Atsushi Matsui, Reina Tsuda, Koichiro Shinoda, Hirofumi Taki, Kazuyuki Tobe  
First Department of Internal Medicine, University Toyama

Conflict of interest: None

A 24-year-old man with systemic lupus erythematosus (SLE) was admitted to our department because of high grade fever, headache, and vomiting. He was diagnosed with SLE according to the presence of polyarthralgia, lymphocytopenia, anti-nuclear antibody and anti-RNP/Sm antibodies for 2 years and his condition was stable with low dose prednisolone (PSL). A month before admission, he suffered hemophagocytosis of unknown etiology and the treatment of corticosteroid pulse therapy and daily trimethoprim-sulfamethoxazole (TMP/SMX: 80mg/400mg) for prophylaxis of pneumocystis pneumonia was started. He had been successfully treated and the dose of PSL was tapered to 30mg/day and discharged. A routine lumbar puncture performed on admission revealed an abnormally elevated leukocyte count, and meningitis was suspected. He was treated empirically with MEPM, ABPC, VCM, AMP-B, and dexamethasone with the discontinuation of TMP/SMX. Since viral, bacterial, and fungal cultures were negative, a diagnosis of aseptic meningitis was made. He had recovered without any complication. The lymphocyte stimulation test for TMP/SMX gave a positive result and we diagnosed possible TMP/SMX induced aseptic meningitis. We discuss about TMP/SMX induced aseptic meningitis and the association with SLE.

### P3-151

#### **A case of SLE developing after contracting mycoplasma pneumonia**

Takaya Ozeki<sup>1</sup>, Takahiro Imaizumi<sup>2</sup>, Yoshiro Fujita<sup>3</sup>

<sup>1</sup>Department of Nephrology, Toyohashi Municipal Hospital, Toyohashi, Japan, <sup>2</sup>Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan, <sup>3</sup>Department of Rheumatology, Chubu-Rosai Hospital, Nagoya, Japan

Conflict of interest: None

[Case] A 22 year old woman was admitted to our hospital because of prolonged fever for 3 weeks. She also had cough, arthralgia, livedo reticularis, numbness of both feet. Measured autoantibodies were negative. She had infiltrates and pleural effusion in both lungs. Because mycoplasma antibody was positive, she was treated as mycoplasma pneumonia. After starting the antibiotics, respiratory status and lung infiltration was improved, but the other symptoms showed no remarkable change. We assessed her as AOSD developed in response of mycoplasma pneumonia and administered steroid. Then, the fever disappeared and other symptoms also improved. After about one year, re-examination of autoantibodies revealed that antinuclear antibody and anti-DNA antibody turned positive. After few days, she exhibited high fever, chest pain and dyspnea. She had the pericardial and left pleural effusion. She was diagnosed SLE. We started glucocorticoid therapy (PSL: starting at 30mg / day). After that, fever and serositis were improved. She has been kept well by tapered steroid and mizoribine. [Conclusion] Mycoplasma pneumonia can be a trigger of SLE onset. And if the patient is clinically suspected SLE, it is necessary to carefully follow-up even though antinuclear antibody is negative.

### P3-152

#### **Early diagnosis and multidisciplinary treatment of catastrophic antiphospholipid syndrome contributed to the suppression of the organ failure**

Tetsu Itami, Kenji Sakai, Shinkai Ri, Chiemi Tasaki, Asuka Inoue, Taeko Yumoto, Toshihiko Shiga, Kayo Asato, Tomohiro Yano, Shoichi Hino, Kazuya Kishimoto, Hideki Shimazu, Yatsuaki Nagare, Yuji Nozaki, Koji Kinoshita, Masanori Funouchi, Itaru Matsumura  
Kinki University Faculty of Medicine

Conflict of interest: None

(Case and History) A-18y,o female was healthy until February 2014

when facial butterfly rash occurred. Then she was admitted to our hospital. On the time, there were no remarkable symptoms including neurological abnormalities, edema or hypertension. She was diagnosed as having systemic lupus erythematosus (SLE) according to the classification criteria; arthritis, proteinuria, pancytopenia and positive serum anti-double stranded DNA antibody. There was a severe renal dysfunction (glomerular filtration rate [eGFR] 53ml/min/m<sup>2</sup>) as well as positive test for serum anti-cardiolipin antibody and lupus anti-coagulant. On ophthalmological examination, there were soft exudates and retinal bleeding. Echocardiography revealed thrombi attached to the mitral valve, and there were multiple small cerebral infarctions in the image of the brain MRI. Since catastrophic anti-phospholipid antibody syndrome was suspected, she was administered with multidisciplinary treatment, followed by improvement in the renal function and multiple small cerebral infarctions. (Conclusion) CAPS develop in short period with poor prognosis. In this case, we could make an early diagnosis of CAPS and performed multidisciplinary treatment according to CAPS Registry, which seemed to contribute to prevent organ failure.

### P3-153

#### **A case of patient of systemic lupus erythematosus who developed with disturbance of consciousness and peripheral neuropathy due to treatment with etanercept in rheumatoid arthritis**

Amane Nakabayashi<sup>1</sup>, Yu Isoda<sup>1</sup>, Aiko Tominaga<sup>1</sup>, Tomoya Sagawa<sup>1</sup>, Akiko Kasahara<sup>1</sup>, Risa Sagawa<sup>1</sup>, Takashi Kida<sup>1</sup>, Kazuki Fujioka<sup>1</sup>, Yuji Kukida<sup>1</sup>, Wataru Fujii<sup>1</sup>, Ken Murakami<sup>1</sup>, Takahiro Seno<sup>1,2</sup>, Aihiro Yamamoto<sup>1</sup>, Masataka Kohno<sup>1</sup>, Yutaka Kawahito<sup>1</sup>

<sup>1</sup>Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>2</sup>Department of Rheumatic Diseases and Joint Function, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: None

[Case] 48-year-old, female [Current history] She was diagnosed with scleroderma in 2009 and rheumatoid arthritis (RA) in 2012. She had been treated with etanercept (ETN) 50mg/week and methotrexate (MTX) 4mg/week. High-grade fever appeared from November 2013. Therefore, ETN and MTX were discontinued and PSL20mg/day were started. But it was poor to improve her clinical condition. She lose her appetite and was able to hardly move. Then left foot drop appeared and fell down. She was suspected of systemic lupus erythematosus (SLE) due to anti ds-DNA antibody positive, low complement in the blood exam, and was admitted to her nearby hospital. She was accompanied by disturbance of consciousness and decrease in activity of daily life. Since renal dysfunction and T2 hyperintense area was recognized in the left medulla by head MRI, steroid pulse therapy and PSL 60mg/day were given. However it offered little benefit, she transferred to our hospital on december 25. We diagnosed with CNS lupus, and plasma exchange and IVCY made her level of consciousness and peripheral neuropathy gradually improve. Cerebrospinal fluid examination findings were also improved. [Conclusion] We experienced a case of SLE who developed with disturbance of consciousness and peripheral neuropathy due to treatment with etanercept in RA

### P3-154

#### **Clinical characteristics of thrombotic thrombocytopenic purpura (TTP) in patients with collagen vascular disease (CVD)**

Tomoyuki Ito<sup>1</sup>, Hajime Yamazaki<sup>1</sup>, Yoko Wada<sup>2</sup>, Takako Saeki<sup>1</sup>

<sup>1</sup>Internal Medicine, Nagaoka Red Cross Hospital, <sup>2</sup>Division of Clinical Rheumatology and Nephrology, Niigata University Graduate School of Medical and Dental Sciences

Conflict of interest: None

We reviewed the medical records of 4 patients (1 male, 3 females) with CVD diagnosed as having TTP based on the classical 'pentad' of symptoms and with an ADAMTS13 activity of <5% seen at Nagaoka Red Cross Hospital between December 2002 and July 2014. Three patients with SLE and 1 with MCTD were identified. At onset of CVD, three patients showed positivity for anti-RNP antibody. Among the patients with SLE, 2 had an elevated level of anti-dsDNA antibody and 1

was complicated by WHO class IV lupus nephritis. All patients achieved remission with only steroid therapy, and remission had been maintained with a low dose of oral prednisolone (PSL) until just before onset of TTP. The disease duration of CVD until TTP onset had ranged from 2.2 to 23.8 years. At onset of TTP, all of the patients were negative for antiphospholipid antibodies. A marginally low compliment level and a mildly elevated level of anti-dsDNA antibody remained unchanged in one patient each. All of the patients were treated with plasma exchange and high-dose oral PSL, and 2 of them received steroid pulse therapy. All patients achieved remission and 3 showed no relapse for over 1 year. It should be borne in mind that TTP, especially in the form of SLE, can occur in patients with inactive CVD.

### P3-155

#### The retrospective study of SLE patient's reason for hospitalization

Yuzuru Yamamoto, Yoshikazu Fujikawa, Yumiko Nobuhara, Takashi Nakazawa

Department of Rheumatology Osaka Saiseikai Nakatsu Hospital, Japan

Conflict of interest: None

**[objective]** We examined the cause and background factor at the time of SLE patient's hospitalization. **[method]** We retrospectively examined the SLE in April 2013 to September 2014 in Osaka Saiseikai Nakatsu Hospital. **[Results]** They were a total of 40 cases for 22 persons. 3 males and 19 females, Age average; 38.6, range; 16-78 y.o. average disease duration was 5.07 years (2 months to 26 years). The 12 examples of new onset had the symptoms specific for SLE, (rash (10), nephritis, blood cell reduction (7), arthritis (6), pericarditis (5), enteritis, lymphadenitis (3 each), NPSLE, pneumonia (1), hypocomplementemia (11)). The reasons for hospitalization for 25 cases 7persons are cyclophosphamide pulse therapy (IVCY) and adverse events due to immunosuppressive therapy. Four flare cases were new onsets of enteritis (2) and flare of nephritis (2), and they were improved under additional treatment. The adverse events consist of 5 of infection and 6 of non-infectious diseases. **[conclusion]** The new onset of SLE patients' reasons for hospitalization are often lupus nephritis, and for the relapse cases, too. Our experience of 4 cytopenic cases due to immunosuppressant calls us attention to be careful for the stable out patients.

### P3-156

#### Severe SLE similar to Meigs syndrome

Hiroyuki Akebo, Shuko Hashimoto, Teruhisa Azuma, Hiroyasu Ishimaru, Kazuhiro Hatta

General Internal Medicine, Tenri Hospital, Nara, Japan

Conflict of interest: None

A 46-year-old female was complaining about a 3-day history of progressing facial edema. She was admitted because of severe nausea. **[Physical examination]** Face: extremely edematous **[Laboratory studies]** Alb 2.9 g/dl, CRP undetectable **[Contrast enhanced CT]** Left ovarian cystic lesion with contrast enhanced area, pleural effusion and ascites **[Clinical course]** Meigs syndrome was suspected as the pleural effusion and the ascites were exudative. Contrast enhanced MRI revealed left ovarian mass was completely cystic. Additional laboratory studies revealed lymphocytopenia, low complement, positive for anti-ds-DNA and anti-Sm antibodies. She was diagnosed as SLE and administered 0.5 mg/kg/day of prednisolone (PSL) on the 5th day. The nausea was improved but the edema remained. She showed generalized seizures with lymphocyte dominant pleocytosis in the cerebrospinal fluid on the 10th day. She was diagnosed as SLE associated meningitis and administered 1 g/day of methylprednisolone for 3 days and 500 mg/body surface area of intravenous cyclophosphamide followed by the treatment with 1 mg/kg/day of PSL. She did not show seizures again. The pleural effusion and the ascites disappeared. **[Clinical importance]** Laboratory studies are essential to distinguish SLE from Meigs syndrome.

### P3-157

#### Outcomes of mycophenolate mofetil treatment for systemic lupus erythematosus

Masanori Kono<sup>1</sup>, Hiroyuki Yamashita<sup>1</sup>, Yuko Takahashi<sup>1</sup>, Hiroshi Kaneko<sup>1</sup>, Toshikazu Kano<sup>2</sup>, Akio Mimori<sup>1</sup>

<sup>1</sup>Division of Rheumatic Diseases, National Center for Global Health and Medicine, Tokyo, Japan, <sup>2</sup>Division of Rheumatic Diseases, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan

Conflict of interest: None

**[Objectives]** Mycophenolate mofetil (MMF) therapy is widely used, especially for lupus nephritis (LN) in Western countries, but its use is limited in Japan. We examined the efficacy of MMF for SLE in our department. **[Methods]** We retrospectively studied 20 SLE patients treated with MMF. MMF use was unavoidable in all cases because of intolerance to intravenous cyclophosphamide (IVCY) or the need to preserve fertility. **[Results]** There were 13 cases of LN, 3 of NPSLE, 1 of arthritis and malar rash, 1 of AIHA, and 2 of other conditions. All LN cases except 1 were in remission for up to 56 months. LN relapsed after cessation of MMF in 1 case. IVCY was switched to MMF 1500 mg daily because of hematuria in a patient with rapidly progressive glomerulonephritis (RPGN), resulting in remission after 3 months. 1 case with acute confusional state, treated with steroid pulse therapy and MMF, experienced relapse after MMF dose tapering. Remission was noted in the other NPSLE cases. The steroid dose was tapered without relapse in patients with arthritis and malar rash and AIHA who were switched from tacrolimus to MMF. **[Conclusion]** MMF was effective for achieving remission in patients with LN, RPGN, and extra renal manifestations. However, the time at which the MMF dose should be tapered is unclear.

### P3-158

#### A case of systemic lupus erythematosus complicated with insulinoma presenting consciousness disturbance, convulsion and hypoglycemic episode

Yasushi Koyama, Noriko Sasaki, Takayoshi Kurabayashi, Sho Sasaki, Shinichi Nogi, Kiri Honda, Chiho Yamada, Shinji Sato, Yasuo Suzuki  
Department of Internal Medicine Division of Rheumatology Tokai University School of Medicine

Conflict of interest: None

Here we report a case of systemic lupus erythematosus (SLE) and insulinoma presenting recurrent consciousness disturbance, convulsion and hypoglycemic episode. In 2009, she was diagnosed as SLE because of fever, polyarthritis, pancytopenia and positivity of anti-nuclear antibody and anti-dsDNA antibody. In July 2014, she was transferred to our hospital due to fever, consciousness disturbance, the elevation of muscle enzyme and abnormal shadows on lung fields. At first, she was suspected to have pneumonia and antibacterial agent was started. However, consciousness disturbance did not improved and she was diagnosed as CNS lupus based on further examination including spinal fluid examination. Treatment with methyl- prednisolone (PSL) pulse and intermitted intravenous cyclophosphamide therapy (IVCY) was initiated and symptoms were improved. During the tapering of PSL, she began to experience hypoglycemia, consciousness disturbance and convulsion. Although the exacerbation of CNS lupus was suspected, PSL and IVCY therapy was not effective. Finally, results of abdominal CT and arterial stimulation and venous sampling provided confirmation of the diagnosis as insulinoma. In this case, it was difficult to make the diagnosis of insulinoma because she was under treatment of CNS lupus.

### P3-159

#### A case of severe neutropenia in patient with systemic lupus erythematosus

Atsushi Matsui, Hiroyuki Honoki, Satoshi Yamaguchi, Koichiro Shinoda, Hirofumi Taki, Kazuyuki Tobe

1st Department of Internal Medicine, University of Toyama

Conflict of interest: None

A 65 year-old woman was referred to our department for the treat-

ment of interstitial lung disease (ILD). She had morning stiffness, xerostomia and photosensitivity. Laboratory data showed leukocytopenia (WBC 3310/ $\mu$ l) and hypocomplementemia. Anti-nuclear antibody, anti-RNP/Sm antibody and anti-SS-A antibodies were positive. She was diagnosed with systemic lupus erythematosus (SLE), Sjögren's syndrome (SJS) and ILD complicated with SLE/SJS. Although her white blood cell count was low, blood differential test showed not lymphocytopenia but severe neutropenia (about less than 500/ $\mu$ l). Then she was treated for cellulitis with antibiotics, however G-CSF was not used because G-CSF was reported to possibly associate with lupus flares. Bone marrow biopsy showed hypocellular marrow without evidence of malignancy. Although antineutrophil antibody was not detected, her neutrophil counts were increased to normal ranges about 8000/ $\mu$ l after corticosteroid pulse therapy for ILD. Given the sensitivity for antineutrophil antibody, the neutropenia was considered to be due to not only suppressed bone-marrow or maldistribution, but also due to autoimmune mechanism. We discuss about neutropenia in autoimmune disease and also discuss the management of severe neutropenia in SLE with literature review.

### P3-160

#### **A case of systemic lupus erythematosus complicated by Coombs-negative hemolytic anemia**

Tepei Kamikawa<sup>1</sup>, Muneo Ota<sup>1</sup>, Teruchika Yamada<sup>2</sup>, Yuichi Handa<sup>1</sup>  
<sup>1</sup>Saitama Red Cross Hospital, <sup>2</sup>Omiya Clinic

Conflict of interest: None

[Case] An 81-yo woman with the chief complaint of lightheadedness, had developed SLE at 60 years, PSL7.5mg was administered before admission. On June 21, she felt lightheaded and was transported to our hospital. Because blood tests revealed marked anemia (Hb 3.3mg/dL), she was admitted on the same day. [Course] After admission, the patient's Hb level temporarily increased with blood transfusion but subsequently decreased. Gastrointestinal bleeding-related anemia was excluded after normal findings on upper gastrointestinal endoscopy. The Coombs test result was negative, but a marked decrease in haptoglobin level indicated hemolytic anemia. We first suspected Coombs-negative autoimmune hemolytic anemia; however, red cell-bound immunoglobulin G level was normal. Next, the patient was screened for low-titer cold agglutinin disease (CAD); cold agglutinin titer was 8-fold at 4°C and negative at  $\geq 25^{\circ}\text{C}$ ; and CAD was confirmed. After increasing the PSL dose to 20 mg, her Hb level stabilized. Because her general condition had stabilized, she was transferred to another hospital on September 9. [Conclusion] SLE complicated by CAD-induced hemolytic anemia resolved after steroid treatment. This case is an interesting example for differentiating anemia associated with SLE.

### P3-161

#### **A case that was complicated the venous thrombosis/the pulmonary thromboembolism after the renal biopsy to the lupus nephritis and suspected of the low-dose pill as the cause**

Naoaki Ito<sup>1</sup>, Takuya Hirai<sup>1</sup>, Kozo Watanabe<sup>1</sup>, Kana Tanji<sup>1</sup>, Keigo Ikeda<sup>1</sup>, Shinji Morimoto<sup>1</sup>, Yoshinari Takasaki<sup>2</sup>, Iwao Sekigawa<sup>1</sup>  
<sup>1</sup>Department of Internal Medicine and Rheumatology, Juntendo University Urayasu Hospital, Chiba, Japan, <sup>2</sup>Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan

Conflict of interest: None

A case is a 45 years-old woman. She was diagnosed as SLE 13 years ago. She was treated in the PSL 20mg after the steroid pulse therapy, and had been maintained by PSL 3mg. She had also serious dysmenorrhea and she had taken the low-dose pill (norethisterone ethinylestradiol tablet). The urine protein and the hypocomplementemia appeared a month ago. After the admission, she was received the renal biopsy, and the next day, she suffered from dyspnea after the rest cancellation. Both the hypoxia and the blood pressure drop were recognized. There was the venous-heart stress remarked by the ECG and cardiac ultrasound test. We observed the imaging poor region in the pulmonary trunk and the left-lower thigh venula by enhanced CT. We diagnosed as the venous thrombosis and the pulmonary thromboembolism. We started injection of the heparin and all symptoms were improved. There was neither the coagula-

tion-factor paucity nor the antiphospholipid antibody. We considered the prolonged recumbency and the long-term steroid therapy as the thrombotic factor. Especially, the low-dose pill was strongly suspected of the cause. There are various opinions about the use of the low-dose pill for SLE patients, so we will report with bibliographic considerations.

### P3-162

#### **Klinefelter syndrome in a patient with systemic lupus erythematosus**

Tsuneaki Yoshinaga, Wataru Ishii, Shuichi Ikeda  
Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Matsumoto, Japan

Conflict of interest: None

A 62-year-old man with a 10-year history of SLE showed nasal bleeding and thrombocytopenia (24,000/ $\mu$ l), and was admitted to our hospital. He had gynecomastia, and laboratory data showed pancytopenia (WBC 1,400/ $\mu$ l, and Hb 9.9g/dl). Bone marrow aspiration was performed. The bone marrow smear showed normocellular marrow, but G-banding test showed 47, XXY karyotype. He was diagnosed as having Klinefelter syndrome (KS). Further evaluation showed the delay of secondary sexual characteristic, infertility, and a low serum testosterone level. KS is present in about 1 of 700 male infants. Some cases of KS seem to be underdiagnosed. Previous report showed that five of the 213 men with SLE had KS (2.4%). And the risk of SLE in men with KS is predicted to be similar to the risk in normal women with 46, XX and about 14-fold higher than in men with 46, XY. This case highlights that infertility and gynecomastia seen in male patients with SLE represent the possibility of KS.

### P3-163

#### **Two cases of systemic lupus erythematoses (SLE) which it was accompanied with specific clinical condition and hemolytic anemia**

Shin Furukawa, Hirohiko Kitakawa  
Internal Medicine, Kushiro Red Cross Hospital

Conflict of interest: None

[Objectives] Report about 2 SLE cases with hemolytic anemia. [Methods] Case report. [Results] Case 1): 44 years old male. He was diagnosed as anemia and showed reticulocytosis, LDH high, haptoglobin low level. We detected warm antibody / cold antibody by Coombs examination and doubted mixing-related hemolytic anemia. He merged renal dysfunction with proteinuria, and antinuclear antibody were positive, and we diagnosed it as SLE of mixed type AIHA. We started steroid therapy for treatment for him. In addition, we used IVCY therapy and it remitted it. Case 2): 18 years old female. Examination showed pancytopenia / nephrotic syndrome / anti-DNA antibody high, and we diagnosed her as SLE. Because we showed extensive urine protein, renal function degeneracy, we performed steroid pulse therapy for her. We thought about thrombotic thrombocytopenic purpura (TTP) and started plasma pheresis (PE). The data were restored after PE, but it was ADAMTS13 activity 147%, and she was clinical condition of atypical hemolytic uremic syndrome (HUS). We diagnosed it as thrombotic microangiopathy symptom by steroid fastness SLE (TMA) and started IVCY therapy for her. Blood platelet was normalized in data, and renal function was improved. [Conclusion] Further consideration will be needed for SLE with hemolytic anemia.

### P3-164

#### **A case of systemic lupus erythematosus, which became a diagnosis from abdominal symptoms with spontaneous remission and exacerbation Repeatedly**

Yu Isoda, Yasunori Tsubouchi  
Division of Internal Medicine, Kyoto Kuramaguchi Medical Center

Conflict of interest: None

SLE is an autoimmune disease which presents a variety of organ diseases. If the main symptom is abdominal, not a few cases the differential diagnosis of a gastrointestinal disease, including ileus and appendicitis is

difficult. [case]19-year-old woman. She consulted a doctor at a nearby medical clinic, complaining of swelling and pain in the abdomen. Her symptoms were temporarily improved by the fasting and symptomatic treatment, but soon came down with the same symptom and was sustained thereafter. Because it showed massive ascites and a wide range edema in small intestine by abdominal contrast CT, she was referred to our hospital.

### P3-165

#### **A Case of neuropsychiatric-lupus successfully treated with intravenous cyclophosphamide therapy for an acute confusional state (delirium)**

Hidetaka Ishino

North Medical Centre Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: None

[Background] Neuropsychiatric systemic lupus erythematosus (NPSLE) is serious complications as with lupus nephritis in systemic lupus erythematosus (SLE). [Case] A 40-year-old female, who had been receiving treatment for anxiety neurosis, manic-depressive since she was 30 years old by other psychiatric clinic. She came complaining of sore throat and developed a high-grade fever in 2013. She was admitted to hospital, high grade fever, joint pain, dermatoid. She was diagnosed, had Neuropsychiatric systemic lupus erythematosus (NPSLE), treated with high-dose steroids, IVCY, and cyclosporine. She recovered unassisted walking after combination therapy with high-dose steroids, IVCY, and cyclosporine. This is a suggestive case of neuropsychiatric lupus successfully treated with multi-target therapy with high-dose steroids, IVCY, and cyclosporine.

### P3-166

#### **A case of normotensive systemic scleroderma renal crisis induced by immune complex nephritis and MPO-ANCA changed to positive**

Masao Tamura, Makoto Terada, Yuko Kashihara

Itami Hospital, Hyogo, Japan

Conflict of interest: None

Case report A 64-year-old woman had Raynaud phenomenon, sclerosis of skin, and positive anti Scl-70 antibody. A CT scan revealed pulmonary fibrosis. These results indicated systemic sclerosis (SSc). MPO-ANCA was negative at first. In April 2013, she admitted presenting with proteinuria, microscopic hematuria, renal insufficiency and polyarthralgia. Laboratory findings showed elevation of serum CRN level (1.86 mg/dl) and a high titer of MPO-ANCA (>300 EU). On the other hand, she had not a hypertension. Renal biopsy revealed mesangial IgM and C3 deposits by IF, but typical features of glomerulonephritis with crescent formation did not exist. The patient was diagnosed with normotensive scleroderma renal crisis, which is a very limited subset of scleroderma renal crisis showing normotensive acute renal failure secondary to MPO-ANCA-associated glomerulonephritis in a patient with SSc. She received prednisolone (40mg/day) and intravenous pulses of cyclophosphamide therapy. These treatment resulted in an improvement of renal function and a marked decrease in hematuria, proteinuria and MPO-ANCA titer. This is an usual case of SSc complicated with immune complex nephritis and normotensive systemic scleroderma renal crisis.

### P3-167

#### **Disappearance of autoantibodies to RNA polymerase III in a patient with systemic sclerosis successfully treated with prednisolone and methotrexate**

Kazumitsu Sugiura, Yoshinao Muro

Department of Dermatology, Nagoya University Graduate School of Medicine

Conflict of interest: None

A 66-year-old man exhibited Raynaud's phenomenon in the fingers. Four months later, oedema of the bilateral hands and feet and polyarthral-

gia occurred. A half-year after the initial episode of Raynaud's phenomenon, the patient was admitted to our hospital with severe joint pain and the inability to walk unaided. He had no particular past history. The modified Rodnan TSS was 16. There was bone marrow oedema in the carpal bones. He had no remarkable finding for internal organs. Anti-RNAP III was detected by ELISA with a high index at two points. The patient was diagnosed as having SSc. We administered systemic PSL at 30 mg/day and MTX at 6 mg/week. The TSS fell to 0 in 6 weeks. PSL has been tapered to 5mg, and MTX at 8 mg/week has been continued; however, no recurrence of skin sclerosis or arthralgia, or even of Raynaud's phenomenon has occurred for 3 and half years. Anti-RNAP III became negative with ELISA about 1 year after treatment was started. [Clinical significance] It is extremely rare for anti-RNAP III to become negative after treatment in patients with SSc. We assume that the extremely positive response to the treatments for SSc, to the extent of completely resolving the Raynaud's phenomenon, might be related to the disappearance of anti-RNAP III.

### P3-168

#### **Two cases of large vessel thrombosis complicated with scleroderma**

Haruo Yamanaka, Teruhisa Azuma, Shuko Hashimoto, Hiroyasu Ishimaru, Kazuhiro Hatta

Tenri Hospital

Conflict of interest: None

[Case]79-year-old Japanese woman was diagnosed as a scleroderma (RNP positive) thirty years ago and rheumatoid arthritis a year ago, respectively. She was suffering from severe sharp pain of the left leg for one week. Ultrasonography revealed that her superficial femoral artery (SFA) was obstructed by a thrombus-like echo lesion. She was unsuccessfully treated with medications. On the 3 admission day, a 4cm white thrombus in her left SFA was removed by surgical intervention and percutaneous thrombus aspiration and transluminal angioplasty (PTA) was also carried out, which led to improvement in her sharp pain of left leg. [Case 2]58-year-old Japanese man was diagnosed as a scleroderma (Scl-70 positive) 10 years ago. He developed sharp pain of his right leg on exertion one week before hospitalization. His ABI at admission was not detected at right leg. He was unsuccessfully treated with medications. At 18 admission day, after failure of surgical thrombectomy, PTA was successfully carried out. After PTA, his ABI recovered to 0.97. [Conclusion] The vascular lesion of scleroderma is considered to be occurred by obstruction of capillary and arteriole. However, we observed two cases of the obstruction of great vessels concurrent with a scleroderma.

### P3-169

#### **A case of scleroderma presenting with symptoms of polymyalgia rheumatica-like by osteomyelitis**

Yasunori Tsubouchi, Yu Isoda

Division of Internal Medicine, Kyoto Kuramaguchi Medical Center, Kyoto, Japan

Conflict of interest: None

[Case] The patient was 78-year-old woman. She was prescribed cefaclor oral, but fever, shoulder pain, and hip pain did not improve. Because WBC and Serum CRP level was high, she was admitted to our hospital. We considered polymyalgia rheumatica in order to meet the diagnostic criteria of Bird et al. Shoulder contrast MRI did not show bilateral scapulothoracic periarthritis and subacromial bursitis. Pelvic MRI showed bone marrow edema changes and fracture line in both sides pubic bone, the acetabular. So we diagnosed pubic bone fractures and osteomyelitis, and gave Ceftriaxone infusion to her. Fever and shoulder pain disappeared. WBC and Serum CRP level decreased to normal range. Hip pain was disappeared by treatment with Risedronate oral and Elcatonin injection. ANA and anti-centromere antibody, finger skin curing and Raynaud's symptoms showed that she was suffering from scleroderma. [Consideration] Antibiotic oral therapy was invalid and her symptom was similar to the polymyalgia rheumatica. But we diagnosed osteomyelitis by imaging, and antibiotic drip treatment was successful. The presence of scleroderma was revealed by autoantibody measurement. If polymyalgia rheumatica is suspected, it is necessary to perform a differential

diagnosis as well before initiation of therapy.

### P3-170

#### A case of anti-CCP positive mixed connective tissue disease treated with abatacept

Hirokazu Takaoka<sup>1</sup>, Tadashi Nakamura<sup>1</sup>

<sup>1</sup>Section of Internal Medicine and Clinical Rheumatology, Kumamoto Shinto General Hospital, <sup>2</sup>Section of Internal Medicine and Hematology, Kumamoto Shinto General Hospital

Conflict of interest: None

A 36-year-old woman had bilateral wrists swelling in November 2013. At first diagnosed as rheumatoid arthritis she had been treated with salazosulfapyridine, her symptom got improved. But it was discontinued for hepatopathy from June 2014. She was admitted to a hospital with myalgia and high level of CPK in late September. She had not muscle weakness but myalgia in proximal muscle, in laboratory data, CPK was 2352 IU/L, RF was 301 U/ml, anti-CCP was 101 U/ml, ANA was 1280, anti-RNP was over 500 U/ml, and anti-Jo-1 was negative. Magnetic resonance imaging of the wrist was normal, and muscle biopsy revealed loss of myofiber and the much infiltration of CD4 positive T-lymphocyte around it with electron microscope analysis. With the diagnosis of myositis-based mixed connective tissue disease added anti-CCP positive, abatacept (ABT) 500mg drip infusion was given, which improved her symptom. It is reported that the expression of CTLA-4 in the muscle biopsy of patients with inflammatory myopathies. Another study demonstrated that ABT was effective in refractory steroid-resistant polymyositis. Our case had not muscle weakness and we treated her with ABT on ground of positive anti-CCP, the much infiltration of T-lymphocyte in muscle biopsy, and long-term administration of steroids.

### P3-171

#### A case that was treated effectively with prednisolone for the intractable pulmonary arterial hypertension of the NYHA IV degree with mixed connective tissue disease

Koji Nagai, Takao Kiboshi, Masakazu Sugino  
Aino Hospital

Conflict of interest: None

The case is a 49 years old woman. She was diagnosed as pulmonary arterial hypertension (PAH) in September 2011, and started beraprost, bosentan, diuretics, warfarin. Her condition was improved, but her respiratory symptoms was worse in April, 2014, and recognized estimated pulmonary artery pressure (eRVSP) 95mmHg in cardiac ultrasound, and started combination of the sildenafil. However it was in condition to have remained in eRVSP by 85mmHg, and she was admitted to our hospital in July. Mixed connective tissue disease (MCTD) was diagnosed, based upon Raynaud phenomenon, PAH, antiU1-RNP antibody positive, polyarthritis, and sclerema. She was given 40mg/day (0.75 mg/kg) of prednisolone (PSL) from October. Her A-aDO<sub>2</sub>, eRVSP, BNP, NYHA was improved (NYHA from IV to II degree). The scenery of intractable PAH might have the existence of the collagenosis disease, and like this case, PAH was improved by a diagnosis of MCTD. It is known that pulmonary hypertension may be improved by an immunosuppressive drug such as disease of the participation of inflammation including MCTD, and the control of the primary disease becomes important. We reported this case and reviewed the literatures.

### P3-172

#### A case of MCTD associated with steroid-resistant Evans syndrome

Nobuhisa Hirase

Department of Internal Medicine, Nakatsu Municipal Hospital, Nakatsu, Japan

Conflict of interest: None

A 77-year-old woman had been diagnosed with MCTD at 65 years of age in 2002 based on the presence of Raynaud's phenomenon, finger swelling, pericardial effusion, lung fibrosis, leukopenia and positivity for

anti RNP antibodies. She was treated with a prostaglandin analogue, without prednisolone, and recovered uneventfully. On May 27, 2014, she was admitted to our hospital due to general malaise. The laboratory data on admission were as follows: Hb 4.8 g/dl, Plt  $1.1 \times 10^4/\mu\text{l}$ . She was diagnosed with autoimmune hemolytic anemia, based on a positive direct Coombs test, in addition to Evans syndrome, following the detection of idiopathic thrombocytopenic purpura on a bone marrow examination, and SLE, according to positivity for Lupus anticoagulant. She received treatment with steroid pulse therapy. However, the erythrocyte and platelet counts did not increase. Therefore, eltrombopag and tacrolimus were administered. Thereafter, the erythrocyte and platelet counts gradually increased. A component of Evans syndrome involves partial symptoms of SLE. Some cases have been reported in which eltrombopag and tacrolimus were found to be effective for thrombocytopenia due to SLE. Hence, treatment with eltrombopag and tacrolimus is a therapeutic option for steroid-resistant Evans syndrome.

### P3-173

#### Caused an Adrenal insufficiency due to adrenal infarctions in the patient with mixed connective tissue disease (MCTD)

Yuka Goubaru, Tomoya Miyamura, Shoko Kodama, Makiko Higuchi, Yu Kaku, Masataka Nakamura, Rumi Minami, Masahiro Yamamoto, Eiichi Suematsu

Department of Internal Medicine and Rheumatology, Clinical Research Institute, National Hospital Organization, Kyushu Medical Center, Fukuoka, Japan

Conflict of interest: None

A 44-year-old female patient presented with fever, polyarthritis and abdominal pain on April 2014. Contrast enhanced CT revealed an adrenal hemorrhage, and laboratory test showed positive for ANA. She was received mPSL pulse therapy, and was transferred to our hospital for the additional treatment. She was diagnosed with MCTD from raynaud's phenomenon, swollen finger, positive test for antiU1-RNP antibody elevated, a photosensitivity and a sclerodactylia. Although baseline adrenal function showed normal ACTH level, cortisol showed no response by Rapid ACTH test. At 15<sup>th</sup> days, right-side paralysis were appeared and MRI examinations revealed multiple cerebral infarctions. The serological tests revealed normal APTT value and negative for anticardiolipin antibodies and lupus anticoagulant. Protein S was 117%, Protein C was 192% and AT III was 133%. After administration of steroid and warfarin, her symptoms recovered. Because she had multiple organ infarction infarction, our case indicated thrombotic disease associated with MCTD in spite of negative test for conventional thrombotic factors.

### P3-174

#### The clinical experience of rituximab(RTX) in an anti-Jo-1 antibody-positive patient with dermatomyositis(DM) accompanied by interstitial pneumonia

Takao Kodera, Tomoki Takeda, Yumiko Oka  
Tohoku Pharmaceutical University Hospital

Conflict of interest: None

**Objectives** RTX is an effective medication for various autoimmune diseases. While overseas clinical studies have not demonstrated the effectiveness of RTX for DM, it has been suggested that it might be effective for anti-aminoacyl-transfer ribonucleic acid synthetase antibody-positive patients. We report herein a case of repeated, refractory DM accompanied by interstitial pneumonia treated with RTX in an anti-Jo-1 antibody-positive patient. **Methods** A woman in her 60s, who had a more than 10-year history of DM and had been successfully treated with steroids, immunosuppressants, and high-dose gamma globulin therapy, experienced a recurrence. Due to aggravated renal function and diabetes mellitus, RTX was selected as an alternate therapy. Results Prior to RTX administration, the Jo-1 antibody value was 279, and the KL-6 value was 587. RTX (375 mg/m<sup>2</sup>) was administered twice; two months later, the Jo-1 antibody value decreased to 188, and the KL-6 value increased to 979. **Conclusion** It appeared that RTX was somewhat efficacious because a steroid dose increase was not required with the decreased Jo-1 antibody value in this case. However, RTX is a slow-acting medication, and longer follow-up is

necessary. Therefore, we also report the subsequent course of this case.

### P3-175

#### **A case of severe dermatomyositis and non-alcoholic steatohepatitis complicating psoriasis vulgaris successfully treated with infliximab**

Sho Sasaki, Noriko Sasaki, Takayoshi Kurabayashi, Yasushi Koyama, Shinichi Nogi, Kiri Honda, Chiho Yamada, Shinji Sato, Yasuo Suzuki  
Tokai University School of Medicine

Conflict of interest: None

Here we report a case of severe dermatomyositis (DM) and non-alcoholic steatohepatitis (NASH) complicating psoriasis vulgaris successfully treated with infliximab. He noticed facial edematous erythema and proximal muscle weakness in April 2007. Blood test showed the elevation of creatine kinase (CK) and muscle biopsy revealed he had myositis. He also had the elevation of serum liver enzymes and he was diagnosed as NASH based on liver biopsy specimen. His skin and muscle manifestations were refractory and increase doses of prednisolone (PSL) together with high dose g-globulin therapy (IVIg) were performed repeatedly. In April 2014, he began to notice erythema with scaling on his forearms, elbows and knee. Skin biopsy showed he had psoriasis vulgaris. 5 mg/kg of infliximab (INF) was started for both recurrent DM and psoriasis vulgaris and cutaneous and muscle symptoms gradually improved. Interestingly, the elevation of serum liver enzymes simultaneously improved. In this case, it was suggested that INF was possibly effective for NASH.

### P3-176

#### **Treatment of polymyositis and autoimmune hepatitis with CCR5 antagonist in an HIV-1 infected patient**

Rumi Minami, Soichiro Takahama, Yu Kaku, Masataka Nakamura, Makiko Higuchi, Shoko Kodama, Tomoya Miyamura, Masahiro Yamamoto, Eiichi Suematsu  
Internal Medicine, Clinical Research Institute, National Hospital Organization, Kyushu Medical Center

Conflict of interest: None

An HIV seropositive man aged 40 years, presented with proximal muscle pain and arthralgia. Creatinine kinase (CK), transaminase,  $\gamma$  globulin and anti-nuclear antibody were raised. Muscle and liver biopsy showed lymphoplasmocytic infiltration. He was diagnosed with polymyositis and autoimmune hepatitis with HIV infection. After starting antiretroviral treatment, his CD4 count increased and HIV-RNA decreased under detection limit, but CK and transaminase levels increased further and muscle pain got worse. Then, CCR5 antagonist, maraviroc was added hoping in an anti-inflammatory effect. CK and transaminase levels decreased, but as the response was partial, systemic steroid was started. Two weeks later, the patient's CK and transaminase levels had normalized and muscle pain had improved. The mRNA expression of CCR5, interferon- $\gamma$  and tumor necrosis factor- $\alpha$  in his peripheral CD4 positive T cells were analyzed by real-time RT-PCR. They decreased after adding maraviroc, and interferon- $\gamma$  and tumor necrosis factor- $\alpha$  decreased further after systemic steroid treatment. CCR5 has been reported to regulate T cell function in autoimmune diseases. This case suggests an important role of CCR5 in the pathogenesis of polymyositis and autoimmune hepatitis.

### P3-177

#### **Successful treatment of severe thrombocytopenia with eltrombopag in a patient with dermatomyositis**

Tomomi Sasajima<sup>1</sup>, Izaya Nakaya<sup>2</sup>

<sup>1</sup>Department of Respiratology, Iwate Prefectural Central Hospital, Iwate, Japan, <sup>2</sup>Department of Nephrology, Iwate Prefectural Central Hospital, Iwate, Japan

Conflict of interest: None

Eltrombopag, a thrombopoietin receptor agonist, is a new medication approved for the treatment of immune thrombocytopenia. There are no reports on the use of eltrombopag in patients with thrombocytopenia as-

sociated with dermatomyositis. A 39-year-old woman was admitted to our hospital in May 2014 due to myalgia, muscle weakness, arthralgia and eruptions of extremities and cough for 1 week. Physical examination showed heliotropic eruptions of eyelids, Gottron sign of fingers and eruptions of elbows and knees. Laboratory data were as follows: Plt  $20.3 \times 10^4 / \text{mm}^3$ , LDH 480 IU/L, CK 863 IU/L, ANA and anti-Jo-1 antibody were negative. Chest CT revealed multiple consolidations of both lungs. She was diagnosed with dermatomyositis and interstitial pneumonitis, and treated with prednisolone and cyclosporine A. 3 weeks later, she developed thrombocytopenia ( $1.9 \times 10^4 / \text{mm}^3$ ), and bone marrow aspiration specimens showed normocellular marrow. She was treated with pulse methylprednisolone and her platelet count increased. But 4 weeks later, she developed severe thrombocytopenia ( $3000 / \text{mm}^3$ ) and was resistant to conventional therapies such as pulse methylprednisolone, tacrolimus, intravenous immunoglobulin and platelet transfusion. She responded to eltrombopag with normalization of her platelet count.

### P3-178

#### **A case report of dermatomyositis: Tacrolimus-induced thrombotic microangiopathy**

Koya Okabe, Tomoya Miyamura, Makiko Higuchi, Masataka Nakamura, Shoko Kodama, Soichiro Takahama, Yu Kaku, Rumi Minami, Masahiro Yamamoto, Eiichi Suematsu

Department of Internal Medicine and Rheumatology, Clinical Research Institute, National Hospital Organization, Kyushu Medical Center, Fukuoka, Japan

Conflict of interest: None

A 66-year-old woman presented fever, Gottron's sign, elbow purpura, pain caused by pressure in the thigh in July 2014. The laboratory test revealed increased myofibrillar protein, the MRI showed hyperintense on T2-weighted in the internal and external obturator muscles, muscles of the thigh. The pathological findings showed degenerated fibers of muscles and infiltrative cells, she was diagnosed dermatomyositis. The CT scan showed interstitial lung disease. She received prednisolone (PSL) 50mg/day plus tacrolimus (TAC) 2mg/day, but disease activity was resistant. She had steroid pulse therapy at day 13, but presented general malaise and jaundice at day 19. The laboratory test revealed that LDH 92IU/L, indirect bilirubin 4.4mg/dl, Hb 8.0g/dl, Plt 10000/ $\mu\text{l}$ , red cell fragmentation, kidney damage, low level of ADAMTS 13. Drug-induced thrombotic microangiopathy (TMA) was suspected, and discontinued tacrolimus. She received fresh frozen plasma (FFP) and a hemodialysis. After that, her symptoms improved, fresh frozen plasma were stopped. Many type of drugs induced TMA, specifically TAC induced that at the time of transplantation, but occur infrequently in the rheumatic disease. We keep TMA in mind, when presenting with renal disorder, increasing of LDH and decreasing of Plt.

### P3-179

#### **A case with successful radical surgery for lung cancer associated with dermatomyositis in poor performance states with severe dysphagia**

Toshie Higuchi<sup>1</sup>, Daisuke Suzuki<sup>2</sup>, Naoyuki Gamou<sup>3</sup>, Yoshinobu Koyama<sup>1</sup>

<sup>1</sup>Department of Rheumatology, Center for Autoimmune Diseases, Japanese Red Cross Okayama Hospital, <sup>2</sup>Department of Dermatology, Japanese Red Cross Okayama Hospital, <sup>3</sup>Department of Nephrology, Japanese Red Cross Okayama Hospital

Conflict of interest: None

A 69 year-old man with fever, rash, muscle pain, weakness and difficulty in swallowing was consulted to our department. He was diagnosed with dermatomyositis (DM), and mPSL pulse therapy was initiated. Further examination revealed pulmonary squamous cell carcinoma (cT2aN0M0, Stage1B). Although stage of the cancer allowed radical resection, the surgery could not be done because of his poor performance status (PS) 4, high-dose PSL treatment, existence of aspiration pneumonia, and respiratory function failure. The dose of PSL was tapered while combining with cyclosporine and high-dose  $\gamma$  globulin therapy. After gastrostomy and respiratory functional training, his PS was improved to PS2 and the radical surgery was performed. Currently, he is recovered to PS1.



[Discussion] The prognosis of DM with malignancy is generally poor, and the malignancy rules prognosis of the disease. Although this case was PS4 with dysphagia, PSL was tapered to 20 mg after combination of mPSL pulse, cyclosporine and high-dose  $\gamma$  globulin treatments. The gastrostomy and respiratory functional training were also important to improve his PS. [Clinical significance] Even a poor PS case of DM with malignancy, there will be a chance to have a radical surgery if proper and aggressive treatments are carried out.

### P3-180

#### A case of the occurrence of dermatomyositis in a pregnant patient with type 1 diabetes mellitus

Koichiro Suemori<sup>1</sup>, Hitoshi Yamasaki<sup>1</sup>, Jun Ishizaki<sup>1</sup>, Takuya Matsumoto<sup>1</sup>, Sachiko Onishi<sup>1</sup>, Eiji Sada<sup>2</sup>, Masaki Yasukawa<sup>1</sup>, Hitoshi Hasegawa<sup>1</sup>

<sup>1</sup>Department of Hematology, Clinical Immunology and Infectious Diseases, Ehime University Graduate School of Medicine, <sup>2</sup>Department of Medical Technology, Ehime Prefectural University of Health Sciences

Conflict of interest: None

A 37-year-old pregnant woman with type 1 diabetes mellitus was introduced to our hospital for myalgia, general fatigue and elevation of serum creatine kinase. She was presenting the classical skin rash of dermatomyositis and muscle weakness. Electromyogram showed polyphasic low amplitude and fibrillation. The pathological diagnosis by skin biopsy was interface dermatitis. From these findings, she was diagnosed as dermatomyositis. She did not have interstitial pneumonia and malignancy, and prednisolone (20mg per day) was administered. Her symptoms of dermatomyositis were improved and stable during pregnancy. She delivered a healthy baby without any complications at 40 weeks of pregnancy. Although prednisolone was tapered after delivery, the symptoms of dermatomyositis showed no relapse. The occurrence of dermatomyositis in a pregnant patient with type 1 diabetes mellitus is very rare. Therefore, we report it with a review of the literature.

### P3-181

#### A patient with suspected myositis who showed serum creatine kinase elevation during infliximab therapy for ulcerative colitis

Taisuke Isono<sup>1</sup>, Shunsuke Tsuge<sup>1</sup>, Ichiro Mizushima<sup>1</sup>, Akikatsu Nakashima<sup>1</sup>, Mitsuhiro Kawano<sup>2</sup>

<sup>1</sup>Division of Nephrology and Rheumatology, Department of Internal Medicine, Ishikawa Prefectural Central Hospital, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Kanazawa University Hospital

Conflict of interest: None

**[Background]** Some reports described the patients with inflammatory bowel disease (IBD) accompanied with myositis or the patients who developed myositis related to tumor necrosis factor inhibitor. **[Case]** A 40 year old woman, who had been diagnosed with ulcerative colitis (UC) at the age of 34, was referred to our hospital for the evaluation of serum creatine kinase (CK) elevation. She had received infliximab (IFX) for UC, and serum CK level was elevated at sixth administration of IFX. Although IFX administration was stopped, serum CK remained high. On examination at referral, her physical findings showed neither muscle weakness nor myalgia. Laboratory findings showed serum CK and aldolase elevation (1857 U/mL, 10.9 IU/L, respectively). Examined myositis specific antibodies such as anti-Jo-1 antibody were negative. However, the upper arm muscle biopsy revealed mild inflammatory cell infiltration, necrotic and regenerated fibers, which were consistent with myositis. Corticosteroid (CS) therapy promptly decreased serum CK level. **[Conclusions]** In this case, it is suspected that serum CK elevation was associated with myositis on the basis of muscle biopsy findings and response to CS therapy. We should be cautious of development of muscle disorders during the clinical course of IBD.

### P3-182

#### A case of polymyositis complicated with autoimmune hepatitis and chronic thyroiditis

Ryosuke Yamate<sup>1</sup>, Nozomi Iwanaga<sup>1</sup>, Yoshika Shigemitsu<sup>1</sup>, Yasumori Izumi<sup>1</sup>, Kiyoshi Migita<sup>3</sup>, Atsushi Kawakami<sup>4</sup>

<sup>1</sup>National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan, <sup>2</sup>National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan, <sup>3</sup>National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan, <sup>4</sup>Nagasaki University Graduate School of Biomedical Sciences

Conflict of interest: None

A case is a 35-year-old woman. She visited our hospital because of liver dysfunction in October of 2013. She didn't drink and take any medicine. Serum serologic markers for hepatitis B and C virus were negative. Immunologic study revealed positive ANA and anti-smooth muscle antibody. Liver biopsy revealed parenchymal hepatitis which was compatible with autoimmune hepatitis (AIH) on acute onset. On her first visit, muscle enzyme was elevated. But she had no complaints of muscle symptoms. Though she met the criteria of subclinical chronic thyroiditis, the decrease of thyroid hormone was only a little. In March of 2014, she complained of fever, polyarthralgia, myalgia and muscle weakness. The muscle enzyme was markedly elevated. The needle EMG showed myogenic change. So, she was diagnosed with polymyositis. She received steroid and tacrolimus. Then, CK and liver enzymes decreased and muscle symptoms also improved. Because she had no complaints of muscle symptoms and she met the diagnostic criteria of AIH, it took several months by a diagnosis of polymyositis. We should be careful about the diagnosis of a patient with liver dysfunction. Though the association of AIH with chronic thyroiditis is well known, AIH complicated with polymyositis is rare. So, we report this interesting case.

### P3-183

#### A Case of Iliolumbar Artery Bleeding Associated with Dermatomyositis

Akiko Yoshida, Satoru Onoda, Soichi Yamada, Konomi Ashihara, Satomi Mukai, Megumi Kurumizawa, Daisuke Hirano, Jo Nishino, Kenichi Kato, Shusaku Fukaya, Shunji Yoshida

Fujita Health University School of Medicine, Toyoake, Japan

Conflict of interest: None

A 42-year old man consulted a physician for heliotrope rash and Gottron sign in January 20XX. Dermatomyositis was suspected based on findings such as high serum CPK level, interstitial pneumonia. Due to the mild symptoms, he only underwent observation; however, coughing and muscle weakness developed in March, and he was referred to our hospital on April 4<sup>th</sup>. Symptoms such as several parenchymal infiltration shadows on thoracic CT, high serum ferritin value (21556 ng/ml), and anti-CADM-140 positivity, led to a diagnosis of acute lung injury due to dermatomyositis. As respiratory failure also developed on April 7<sup>th</sup>, a tripartite combination therapy was prescribed, resulting in improvements in muscle weakness and lung failure. A sudden drop in blood pressure occurred on April 14<sup>th</sup>, and iliolumbar arterial bleeding and retroperitoneal hematoma were noted on contrast CT. Hemostasis with arterial embolization was attempted, but hemodynamic recovery was not achieved; the patient died on April 25<sup>th</sup>. **[Conclusion]** Only few cases of arterial bleeding with dermatomyositis have been reported; as this case also showed anti-CADM-140 antibody-positivity, we believe that it adds value to the limited literature on the clinical pathology of anti-CADM-140 antibody-positive dermatomyositis.

### P3-184

#### Improvement of hearing loss in a patient with ANCA associated vasculitis treated with Rituximab

Naoki Matsuoka, Shuzo Sato, Hiroko Kobayashi, Makiko Yashiro, Tomoyuki Asano, Hiroshi Watanabe, Hiromasa Ohira  
Department of Gastroenterology and Rheumatology, Fukushima Medical University School of Medicine, Fukushima, Japan

Conflict of interest: None

An 81-year-old woman admitted to our hospital because of progressive, severe hearing loss for 6 months and elevated serum levels of MPO-ANCA (165 IU/ml) in September 2014. Computed Tomography (CT) of bilateral temporal bones showed exudates of mastoid air cells without

bone destruction. In the end of September 2014 she suffered high fever, temporal headache and cough. Systemic CT showed consolidation in both lower lung fields. Blood test showed elevated CRP levels (22.38 mg/dl) and MPO-ANCA levels (279 IU/ml). Hearing test showed bilateral severe mixed conductive-sensorineural hearing loss (100 dB). After admission she was treated with methylprednisolone pulse therapy (1 g/day) following an oral prednisolone (PSL) of 40 mg/day. Hearing loss continued despite the improvement of inflammatory parameters, therefore Rituximab (RTX, 375 mg/m<sup>2</sup>) was administered to her. One week after the administration of RTX, hearing loss gradually improved. After the second attempt of RTX, hearing test improved up to 70dB and we managed to communicate with her without writing. Treatment with RTX should be considered to induce remission as early as possible in patients with ANCA associated vasculitis even if they are aged patients.

### P3-185

#### Vasculitis treated by RTX instead of IVCY

Aiko Tominaga<sup>1</sup>, Takahiro Seno<sup>1,2</sup>, Takashi Kida<sup>1</sup>, Risa Sagawa<sup>1</sup>, Amane Nakabayashi<sup>1</sup>, Yuji Kukida<sup>1</sup>, Hidetake Nagahara<sup>1</sup>, Wataru Fujii<sup>1</sup>, Ken Murakami<sup>1</sup>, Aihiro Yamamoto<sup>1</sup>, Ryo Oda<sup>3</sup>, Masataka Kohno<sup>1</sup>, Toshikazu Kubo<sup>2,3</sup>, Yutaka Kawahito<sup>1</sup>

<sup>1</sup>Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>2</sup>Department of Rheumatic Diseases and Joint Function, Kyoto Prefectural University of Medicine, Kyoto, Japan, <sup>3</sup>Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: None

A 65-year-old female developed fever and was hospitalized. Antimicrobial agents were not effective, and she got vertigo and hearing loss. She was diagnosed with atypical Cogan's syndrome and treated with prednisolone (PSL). But her condition didn't improve enough, she changed to our hospital. She had the bilateral sensorineural hearing loss, the mild vestibular dysfunction, the nasal septal perforation, the saddle nose, the chronic otitis and no ophthalmic symptom characterized by Cogan's syndrome. We considered her clinical condition as atypical Cogan's syndrome or otitis media with ANCA associated vasculitis. She was administered in combination with intravenous cyclophosphamide (IVCY) biweekly and PSL, which was effective. Unfortunately, after administration of 4<sup>th</sup> IVCY, it revealed that she had the pancreatic endocrine tumor. Therefore, we switched IVCY to Rituximab. Following the combination therapy with PSL and RTX, her hearing ability ameliorated and the vestibular dysfunction sustained improving. We could reduce PSL dose to 10mg/day (0.2mg/kg/day). We thought that RTX appears to achieve a remission of refractory vasculitis. We report a case treated with RTX instead of IVCY, and then we consider whether RTX will become one of the most effective treatment for vasculitis.

### P3-186

#### A case of ANCA-associated vasculitis concurred with clinically amyopathic dermatomyositis

Saki Tsujimoto<sup>1,2</sup>, Yoshio Ozaki<sup>1,2</sup>, Nobuyasu Ishii<sup>1</sup>, Toshiharu Sasaki<sup>1,2</sup>, Minoru Shigesaka<sup>1</sup>, Akihiro Tanaka<sup>1,2</sup>, Keiko Shimamoto<sup>1,2</sup>, Tohru Nishizawa<sup>1</sup>, Hideki Amuro<sup>1</sup>, Yonsu Son<sup>1,2</sup>, Shosaku Nomura<sup>1</sup>

<sup>1</sup>Department of Rheumatology and Clinical Immunology, Kansai Medical University Hirakata Hospital, Hirakata City, Japan, <sup>2</sup>First Department of Internal Medicine, Kansai Medical University, Hirakata City, Japan

Conflict of interest: None

[Case] 68 year-old female who had been treated as Clinically amyopathic dermatomyositis (CADM) with MDA5-antibody suffered with continual fever and general fatigue from September. And her blood examination showed CRP elevation gradually. Since she became aware of numbness and dysesthesia of lower limbs, she was admitted to our hospital. She had drop foot on her right limbs, and result of her electromyography indicated severe axonopathy. She had a diagnosis of mononeuritis multiplex neurologically. Additionally it was reported positivity of urinary protein, uric blood and MPO-ANCA, she was diagnosed as ANCA associated vasculitis (AAV). The administration of 1 mg/kg/day prednisolone

was started after mPSL pulse therapy for induction of remission, which rapidly brought the inflammation and dysesthesia of lower limbs under control. [Conclusion] We report a case of AAV complicated with CADM. Though some have reported suggested that vasculitis was related to the pathophysiology of dermatomyositis, it is unusual that CADM and an ANCA-related vasculitis are complicated. It was thought with a valuable case in considering an etiology of dermatomyositis.

### P3-187

#### A case of Takayasu arteritis with isolated pulmonary involvement

Aki Sakashita, Atsushi Omoto, Akiko Ido, Masatoshi Kadoya, Wataru Fukuda

Center of Rheumatic Disease, Japanese Red Cross Kyoto Daiichi Hospital, Kyoto, Japan

Conflict of interest: None

A 21-year-old man was admitted to a local hospital because of cough and fever, and had a diagnosis of pneumonia. Cough and fever were relieved with antibiotics for a moment, but he was consulted to our hospital because of bloody sputum and chest pain. Serum level of C-reactive protein was 3.3mg/dl, erythrocyte sedimentation rate was 41mm/hr. Antinuclear antibodies and MPO-antineutrophil cytoplasmic antibody (ANCA), PR3-ANCA were negative, HLA typing B51 and 52 were positive. Contrast enhanced computed tomography (CT) demonstrated diffuse wall thickening of pulmonary artery. Magnetic resonance angiography (MRA) demonstrated severe stenosis in middle and descending branch of the right pulmonary artery, but aorta and its branches had no involvement. Positron emission tomography/CT (PET/CT) showed increased 18F-fluorodeoxyglucose (FDG) uptake in the right pulmonary artery. We diagnosed the patient as Takayasu arteritis (TA) and he was treated with PSL 40mg/day. He was responsive to treatment, and CRP improved immediately. Pulmonary arteries involvement is well described in TA, but isolated PA involvement is uncommon and rare. It is important to consider TA when we see patient with respiratory symptoms and pulmonary artery stenosis.

### P3-188

#### A case of polyarteritis nodosa with asymptomatic rupture of gastroduodenal artery aneurysm successfully treated by coiling embolization

Kahori Oshima<sup>1</sup>, Takakazu Hasegawa<sup>1</sup>, Kumiko Umemura<sup>1</sup>, Syunsuke Yokoi<sup>1</sup>, Michita Suzuki<sup>1</sup>, Kyoko Takano<sup>1</sup>, Eiji Nagasawa<sup>3</sup>, Nobuyoshi Minemura<sup>1,2</sup>, Masao Katayama<sup>1</sup>

<sup>1</sup>Nagoya Medical Center, Nagoya, Japan, <sup>2</sup>Tamazensyoen, National sanatorium, Tokyo, Japan, <sup>3</sup>Nagasawa Clinic, Nagoya, Japan

Conflict of interest: None

A 62-year-old man was diagnosed as polyarteritis nodosa (PN) because of fever, abdominal pain, elevated serum CRP level, multiple microaneurysms from angiography and lack of MPO-ANCA and PR3-ANCA in 2009. His condition was almost stable, but serum CRP level has been elevated since beginning of April in 2014 without any symptoms. Enhanced abdominal CT scan showed that a huge aneurysm of gastroduodenal artery existed. Because an infective aneurysm was denied from negative blood culture, it was thought that this aneurysm was caused by PN. Prednisolone (PSL) was increased from 7.5mg/day to 30 mg/day and adding cyclophosphamide and elective coil embolization were considered. However, he suddenly vomited a lot of blood, and went into shock in three days after admission. No intraperitoneal bleeding was found by abdominal CT scan and bleeding from gastroduodenal artery aneurysm was found by gastrointestinal endoscopy. The patient had a coiling embolization in emergency and was successfully treated. After adding cyclophosphamide, serum CRP level became normal and he discharged from hospital.

### P3-189

#### A case of anti-neutrophil cytoplasmic antibody-associated vasculitis complicated with early gastric cancer

Takahiro Yajima<sup>1</sup>, Masao Sato<sup>2</sup>

<sup>1</sup>Department of Nephrology, Matsunami General Hospital, Gifu, Japan,  
<sup>2</sup>Department of Rheumatology, Matsunami General Hospital, Gifu, Japan

Conflict of interest: None

A 60-year-old man who is on hemodialysis because of end-stage renal disease due to anti-neutrophil cytoplasmic antibody (ANCA)-associated nephritis, developed alveolar hemorrhage in February 2013. He was successfully treated with steroid pulse therapy, intravenous cyclophosphamide (IVCY) and plasma exchange. Although 6 course IVCY was performed and PSL was tapered to 20mg/day, MPO-ANCA levels remained high (119U/ml). Then he presented with fever and cough on August 3, chest CT revealed nodules, so he was admitted to our hospital.  $\beta$ D glucan level turned out to be high, he was diagnosed as fungal pneumonia. After FLCZ was administered, symptoms were relieved, and pulmonary nodules showed reduction in size. On the other hand, CEA level was 7.8ng/ml, and upper gastrointestinal endoscopy revealed a poorly differentiated early gastric cancer on gastric angle, laparoscopy-assisted distal gastrectomy was performed on December 6, 2013. The MPO-ANCA level was decreased to 34U/ml about a week after the operation. We report a rare case of ANCA-associated vasculitis complicated with early gastric cancer, MPO-ANCA level was decreased after the operation. We suggest that screening of malignancy is necessary, if ANCA level remains high in spite of the appropriate immunosuppressive therapy.

### P3-190

#### **A case of gradually improving of pulmonary polygranulomatosis after total gastrectomy for gastric cancer**

Eri Okamura, Yumiko Wada, Shuzo Yoshida, Junichi Konma, Takayasu Suzuka, Youhei Fujiki, Nao Tokai, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa

Department of Internal Medicine (I), Osaka Medical College, Takatsuki City, Osaka, Japan

Conflict of interest: None

A 74-year-old man presented with bilateral submandibular swelling, chemosis and elevation of ocular tension from September, 2013. Chest X-ray revealed bilateral lung consolidations and Positron Emission Tomography/Computed Tomography (PET/CT) with fluorodeoxyglucose (FDG) showed uptake of FDG in nasal cavity, bilateral ethmoidal sinus, lacrimal gland, parotid gland, light brachial muscle, and light jaw. C-reactive protein was raised at 9.03mg/dl. Anti-neutrophil cytoplasmic auto-antibody (ANCA) was negative. Serum creatinin was normal. Physical examination showed bilateral submandibular swelling, chemosis, nasal obstruction, and dyspnea. Biopsies of the pulmonary infiltration showed granulomas with giant cell. Based on these findings, he was diagnosed as Granulomatosis with polyangiitis (GPA). At the same time, gastrointestinal endoscopy revealed Bowman's type II progressive gastric cancer. After total gastrectomy which revealed gastric adenocarcinoma, bilateral lung consolidations improved at 6months follow up CT. We presented a case of gradually improving pulmonary polygranulomatosis after total gastrectomy for gastric cancer and review and discuss differential diagnosis of polygranulomatosis.

### P3-191

#### **A case of microscopic polyangiitis with colitis alone**

Mizue Goto, Takahiro Nakayama, Yuta Oyama  
Nihonkai General Hospital, Yamagata, Japan

Conflict of interest: None

[Case] a 55-year-old woman [Clinical course and progress] One week after the patient became rhinitis, she felt the nose swelling and the intense pain in eyes and a nose and she had water diarrhea after that. Computed tomography scan revealed diffuse inflammation in total colon, but a paranasal sinus and lung fields were normal. The renal function and a urinary finding were normal. PR3-ANCA were identified (3.6U/ml). Histological examination of a mucosa biopsy from a colon showed fibrinoid necrosis of the small vessels, but there was no granulomatous lesion. The patient was diagnosed as having MPA severe type with the perforation of gastrointestinal tract. After one course of methyl-prednisolone

pulse treatment (mPSL 500mg/day, orally PSL 1mg/kg/day) and two courses cyclophosphamide pulse treatment tried at intervals of two weeks, resulting in an improvement in the colon lesions. [Conclusion] A very rare case with microscopic polyangiitis with colitis alone without vasculitis of lung and kidney is presented.

### P3-192

#### **A case of eosinophilic granulomatosis with polyangiitis(EGPA) complicating small vessel vasculitis of the liver**

Hiromi Nuka, Kazunori Yamada, Kinya Kitada, Shigeto Horita, Takeshi Zoshima, Satoshi Hara, Kiyooki Ito, Motohiko Aizu, Ryoko Hamano, Hiroshi Fujii, Mitsuhiro Kawano

Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine, Kanazawa Japan

Conflict of interest: None

[Case] 66 years old woman. She was diagnosed as bronchial asthma 10 years ago. She had fever 2 month prior to admission. As numbness of legs and arms gradually developed, she visited a hospital 2 week before admission. At that time, eosinophilia and liver dysfunction were noted and she was referred to our hospital. On admission, she had hypesthesia of legs and muscle weakness of legs and arms. Blood tests showed marked eosinophilia to 26,759 per cubic millimeter and elevation of liver enzymes, AST to 253 U per liter, ALT to 251 U per liter, ALP to 3227 U per liter, and  $\gamma$ -GTP to 333 U per liter. MPO-ANCA and PR3-ANCA were negative. We suspected mononeuritis multiplex, and peroneal nerve biopsy was done. Pathological findings showed small vessel vasculitis with eosinophilic infiltration. Liver biopsy was done and revealed eosinophilic infiltration in portal area and obstruction of hepatic artery with eosinophilic infiltration around artery, without granulomatous reaction and fibinoid necrosis. We made a diagnosis of EGPA and started steroid therapy. Fever and liver dysfunction and eosinophilia quickly resolved, although numbness continued. [Conclusion] We should be aware of hepatic manifestations when liver dysfunction of unknown origin is noted in patients with EGPA.

### P3-193

#### **A case of eosinophilic granulomatosis with polyangiitis manifesting as hepatic failure and diagnosed by liver biopsy**

Satoshi Yamaguchi, Hiroyuki Honoki, Atsushi Matsui, Maiko Obi, Reina Tsuda, Koichiro Shinoda, Hirofumi Taki, Kazuyuki Tobe  
First Department of Internal Medicine, University Toyama

Conflict of interest: None

A 70-year-old man with a history of bronchial asthma was admitted for fever, polyarthralgia, leg edema, and jaundice. He was diagnosed with portal hypertension and bronchial asthma three years ago. On admission, he was febrile and laboratory data showed eosinophilia (7400/ $\mu$ L), hypoalbuminemia, liver dysfunction with severe cholestasis and elevated C-reactive protein. Serum HBs/HBe antigen, anti-HCV antibody, anti-nuclear antibody, anti-mitochondria antibody and anti-neutrophil cytoplasmic antibodies were not detected. His submandibular glands and cervical lymph nodes were enlarged and he had elevated serum IgG4. Leg purpura had appeared and skin biopsy specimens showed leukocytoclastic vasculitis. Liver biopsy was performed and pathological findings demonstrated hepatic fibrosis (F2-F3) and vasculitis of small artery and arteriole with eosinophil infiltration, and he was diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA) and he was successfully treated with prednisolone (60mg/day). In his course, hepatic encephalopathy, cytomegalovirus infection, and MSSA septic shock were occurred, however he recovered well. Hepatic involvement of EGPA manifesting as hepatic failure was extremely rare. We discuss about hepatic involvement of EGPA with literature review.

### P3-194

#### **Churg-Strauss syndrome (CSS) with cardiac failure: 2 cases**

Katsuhiko Oda, Kenichiro Hata, Kentaro Isoda  
Department of Rheumatology, Internal Medicine, Yodogawa Christian Hospital

Conflict of interest: None

[Case 1] A 55-year-old man with asthma had fever, bloody sputum, and leg purpura. Laboratory tests showed eosinophilia and elevated inflammatory response, and MPO-ANCA was positive. He was diagnosed with CSS. He was complicated with renal failure with hematuria and proteinuria, alveolar hemorrhage and cardiac failure. He was successfully treated with mPSL pulse and IVCY. [Case 2] A 22-year-old man with asthma had pain and paresthesias of bilateral lower legs. He was diagnosed with L5/S1 lumbar disk herniation, and admitted for surgery. He had fever and bloody sputum. Laboratory tests showed eosinophilia, elevated inflammatory response, and MPO-ANCA was negative. He was diagnosed with CSS. He was complicated with peripheral neuropathy, alveolar hemorrhage and cardiac failure. He was successfully treated with mPSL pulse and IVCY, but cardiac function remained poor. We administered IVIG and cardiac failure was gradually improved. [Discussion] Cardiac failure with CSS generally has a poor prognosis. We experienced two cases; in one case cardiac failure improved with PSL and immunosuppressant, and in the other case cardiac function remained poor with those treatments, but gradually improved with IVIG. We report with some literature review.

### P3-195

#### **A case of renal involvement in eosinophilic granulomatosis with polyangiitis (EGPA) accompanied by eosinophilic tubulointerstitial nephritis**

Sohei Funakoshi, Hirota Itoh, Masaki Katayama  
Department of Rheumatology, Osaka Red Cross Hospital, Osaka, Japan

Conflict of interest: None

A 52-year-old female had fever, lower leg purpura, paresthesia of limbs, dyspnea. She developed chronic sinusitis and mononeuritis multiplex, and computer tomography (CT) scan demonstrate interstitial pneumonia and alveolar hemorrhage. In laboratory findings eosinophilia, proteinuria, and hematuria was present. Myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) was elevated at 283 U/ml. Skin and renal biopsy showed vasculitis and infiltration of eosinophils. She was diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA). She was treated with methylprednisolone (mPSL) pulse therapy followed by prednisolone (PSL) 50mg/day, and intravenous cyclophosphamide pulse therapy. For presence of alveolar hemorrhage, 7 course of plasma exchange therapy was added. Lung and renal lesions both improved rapidly. At renal biopsy, crescentic glomerulonephritis and tubulointerstitial nephritis eosinophil-rich infiltrated was found. We report a rare case of these histological findings with EGPA.

### P3-196

#### **A case of isolated polyarteritis nodosa appeared in bilateral epididymides and muscle with bilateral scrotums pain**

Takashi Okada<sup>1</sup>, Kentaro Ishiyama<sup>2</sup>, Akira Katagiri<sup>1</sup>, Ken Yamaji<sup>2</sup>, Naoto Tamura<sup>2</sup>, Masato Yamada<sup>1</sup>, Yoshinari Takasaki<sup>2</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Juntendo University Shizuoka Hospital, <sup>2</sup>Department of Internal Medicine and Rheumatology at Juntendo University School of Medicine

Conflict of interest: None

The patient, 71-year-old man, was admitted to our hospital with fever, complaint of painful and swelling bilateral scrotums, and muscle pain of bilateral buttock and thigh during medical treatment in polymyalgia rheumatica. Contrast-enhanced CT showed bilateral hydrocele testis and edema of the spermatic cord. Contrast-enhanced MRI examination showed findings of myositis and fascia flame. He treated for antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs), but there was no improvement. So we performed biopsy from the quadriceps muscle and fascia and right high orchiectomy for the diagnosis and pain control. Pathological findings showed a necrotizing vasculitis, and he was diagnosed as polyarteritis nodosa (PN). After operation, his fever was decreasing, but symptoms of left scrotum did not improve. Therefore we performed left high orchiectomy, and pathological findings showed a necrotizing vasculitis too. Then, his fever went down and the value of

CRP decreased promptly after operation, but muscle pain of buttock and thigh did not improved. After starting treatment with betamethasone 4.0mg/day, symptoms disappeared. It was rare that initial manifestation of polyarteritis nodosa was bilateral scrotum's pain and swelling, and high orchiectomy was useful in such cases.

### P3-197

#### **A case of GPA started with urinary retention and diagnosed by prostate biopsy**

Yuko Ozawa, Akiko Endo, Kyohei Kunizawa, Yoshinori Komagata, Shinya Kaname, Yoshihiro Arimura  
First Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

Conflict of interest: None

A 60-year-old man was admitted in our hospital with urinary retention on Day -4. Blood tests showed leukocytosis and marked inflammation with an elevated CRP. CT scan showed multiple cavitory masses in the lung and an abscess in the prostate. On day 9, the patient needed a treatment with a ventilator suffering from DIC and enlargement of masses, despite of antibiotic therapy. The diagnosis of GPA was made on Day 10 based on high titer of PR3-ANCA (164 U/ml), bilateral sinusitis, hypertrophic pachymeningitis, and histologic findings of necrotizing vasculitis in the prostate. We started mPSL pulse therapy from Day 15 followed by 100mg/day of soluble PSL and IVCY. Although most of symptoms were improved, the patient had a relapse with elevation of serum CRP and new multiple lesions in the lung when the dose of PSL was tapered to 40mg/day. We administered Rituximab on Day 108 and increased the dose of PSL to 60mg/day at the same time, then serum CRP level improved and lung masses shrank. The patient was discharged from our hospital on Day 153. Here we report a rare case of GPA started with urinary retention and diagnosed histologically by prostate biopsy. There are very few case reports of GPA with urinary retention as the first symptom. We also provide a bibliographical review.

### P3-198

#### **A case of antecedent granulomatous vasculitis confined to cervical lesion followed by chronic eosinophilic pneumonia**

Shunichiro Hanai, Yoichiro Akiyama, Ayako Kokuzawa, Koichi Takeda, Katsuya Nagatani, Takeo Sato, Masahiro Iwamoto, Seiji Minota  
Division of Rheumatology and Clinical Immunology, Department of Medicine, Jichi Medical University, Tochigi, Japan

Conflict of interest: None

A 63-year-old woman was referred to our hospital because of swelling in her left neck, fever, and hoarseness, which persisted for two months. An MRI of the neck revealed an enhancing mass. Biopsy showed pathology of vasculitis with granuloma-formation. She was admitted to our division as having possible granulomatosis with polyangiitis (GPA) without organ involvements and MPO/PR3-ANCA was negative. The neck swelling gradually decreased in size spontaneously. However, three weeks after discharge, cough and shadow in chest X-ray appeared, and she was readmitted. A chest CT scan showed infiltrative shadow in bilateral upper areas, and bronchoalveolar lavage fluid and transbronchial lung biopsy revealed infiltration of eosinophils. She was diagnosed with chronic eosinophilic pneumonia (CEP), and oral PSL therapy (50 mg/day) was started. There was no clinical/laboratory findings of GPA or eosinophilic granulomatosis with polyangiitis, and she was diagnosed as having a granulomatous vasculitis localized in her neck, followed by CEP. This case could fit in single-organ vasculitis (SOV) in Chapel Hill Consensus Conference criteria. SOV may progress to systemic vasculitis and meticulous attention be needed.

### P3-199

#### **Polyarteritis nodosa of breast associated with polyarthralgia**

Yoshiko Shimamura, Yoshinori Taniguchi, Tatsuki Matsumoto, Kazuo Ode, Koji Ogata, Shuichi Nakayama, Kosuke Inoue, Makoto Tsugita, Taro Horino, Yoshio Terada

Department of Endocrinology, Metabolism and Nephrology, Kochi Medi-

Conflict of interest: None

**[Case]** A 71 year-old woman presented myalgia and enthesitis of bilateral patellar tendons, fever, weight loss, and admitted to our hospital. On admission, physical findings showed five tender nodules with erythema localized in bilateral breasts. She revealed no skin lesions besides the breast. The laboratory investigations demonstrated elevated levels of C-reactive protein (CRP) 19.8 mg/dl and erythrocyte sedimentation rate (ESR) 124 mm/hour. Biopsy specimen from the nodule of left breast showed the leukocytoclastic medium-sized arteritis without giant cell infiltration, indicating polyarteritis nodosa (PAN). Furthermore, polyenthesitis findings were revealed in patellar tendons, spinous process and ischial tuberosity by FDG-PET/CT and ultrasonography. Therefore, we diagnosed as breast PAN associated with polyenthesitis. Treatment with oral PSL 40mg daily was initiated. Following treatment, her symptoms immediately improved and CRP level also normalized. She was discharged without flare-up. **[Conclusion]** When breast nodules with systemic symptoms including fever and enthesitis were revealed, we always need to consider PAN of breast as one of differential diagnosis.

### P3-200

#### **A case of MPO-ANCA positive Granulomatosis with polyangitis complicated with prevertebral soft tissue mass**

Takumi Matsumoto, Takeshi Kusuda, Shoko Iga, Takahiko Sugihara  
Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan

Conflict of interest: None

**[case]** A 81-year-old woman was diagnosed with otitis media in January 2014, and was admitted to our hospital with a diagnosis of cholangitis in August 2014. Since low grade fever and inflammatory reaction persisted, she was transferred to rheumatology. Refractory otitis media, conjunctivitis, thoracic spine percussion tenderness and interstitial pneumonia were observed, and contrast CT and MRI showed thoracic prevertebral soft tissue masses. MPO-ANCA was 350 IU/ml. FDG-PET showed strong accumulation in the middle ear and the prevertebral lesions. Biopsy was not conducted. Referred to classification algorithm of Watts et al, she was classified as Granulomatosis with polyangitis (GPA) with thoracic prevertebral lesions. Her clinical findings were improved after initial treatment with prednisolone and methotrexate. The size of prevertebral lesions was reduced one month after the treatment. **[Discussion]** We reported a first Japanese case of MPO-ANCA positive GPA with prevertebral lesions. Seven similar cases were reported in Western countries. In these cases, six was PR3-ANCA positive, and one MPO-ANCA positive. Mass lesions were improved in 5 of the 7 cases after immunosuppressive therapy. Prevertebral lesions can be complicated at the onset of MPO-ANCA positive GPA.

### P3-201

#### **A case of the phlebitiss tuberculosa nodosa that was initially suspected of vasculitis in the pathological finding from both lower legs painful tuberculum**

Hiroko Shukuzawa<sup>1</sup>, Takuya Hirai<sup>1</sup>, Kana Tanji<sup>1</sup>, Keigo Ikeda<sup>1</sup>, Shinji Morimoto<sup>1</sup>, Yoshinari Takasaki<sup>2</sup>, Iwao Sekigawa<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Juntendo University Urayasu Hospital, Chiba, Japan, <sup>2</sup>Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan

Conflict of interest: None

A 20-year-old woman was suffered from fever, fatigue, many joint pains, and tuberculums of her both lower legs two months ago. She consulted the dermatology in our hospital, and was received the skin biopsy. There was the remark of the granuloma with vasculitis. Then she was admitted to our department on suspicion of vasculitis. The tubercular IFN- $\gamma$  and the tuberculin-skin-test was positive, and there were enlarged lymph nodes of the neck and the axillaries detected by CT scan. In addition, her father had the hospitalized history by tuberculosis in her childhood term. We carried out the diagnosis to lymph node tuberculosis by the lymph

node biopsy, and diagnosed the tuberculum of her both lower limbs as the phlebitiss tuberculosa nodosa. The anti-tuberculosis drug improved her symptoms. The tuberculoderma is a rare complication in extrapulmonary tuberculosis. Especially, a few cases with the phlebitiss tuberculosa nodosa were reported. Additionally, this case initially suspected of systemic vasculitis was a rare phlebitiss tuberculosa nodosa in the differential diagnosis of vasculitis. We will report with bibliographic considerations.

### P3-202

#### **Case report of GPA who developed Arthritis, Livedo reticularis, Myositis as main manifestations**

Mayuko Moriyama, Yoshiko Sumita, Masahiro Kondo, Yohko Murakawa  
Department of Rheumatology, Faculty of Medicine, Shimanfe University

Conflict of interest: None

A 33-year-old man with a 9 year history of poly-arthritis like Rheumatoid Arthritis (RA). He was treated as RA. He developed Livedo reticularis for 3 years. Laboratory data demonstrated elevated C-reactive protein (CRP) (3.43 mg/dL). Although cytoplasmic-staining anti-neutrophil cytoplasmic antibody was positive, skin biopsy did not reveal vasculitis with granulomatosis. We could not have a definitive diagnosis at that time. He developed marked myalgia in both legs from 3 months before. Serum myogenic enzymes including creatine kinase did not elevate. MRI-STIR showed diffuse high signal intensities on muscles of both thighs and lower legs. Biopsied specimens of tibialis anterior muscle and vastus lateralis muscle showed small vessel vasculitis and granulomatosis. We diagnosed him as having granulomatosis with polyangitis (GPA). Because he had not shown any typical GPA manifestations, we needed time for a diagnosis. Myositis is rare as an initial manifestation of GPA. Our findings suggest that GPA should be considered to the differential diagnosis of diseases associated with myositis.

### P3-203

#### **The case of Polyarteritis nodosa (PN) with mononeuropathy multiplex, following Hemolytic streptococci infection**

Nobuko Iizuka, Yuko Kurihara, Atsushi Suzuki, Takahiro Suzuki  
Department of Inter Medicine, Kawasaki Municipal Ida Hospital, Kanagawa, Japan

Conflict of interest: None

We report a 49-years old man with a history of swellings in lower legs, which diagnosed as vasculitis and observed for 6 years at other hospital. He had sorethroat and fever on this summer and medicated by antibiotics. After 2 weeks, the pain and swells of legs and high-fever appeared. he was admitted to our hospital and taking antibiotics intravenously, and tested skin biopsy. The laboratory examination showed the elevated ASO, WBC, CRP, ESR, IgG and negative ANCA. We diagnosed as polyarteritis nodosa (PN). After prednisolone (1mg/kg) was administered in this patients, the dysesthesia appeared in upper and lower limbs. The EMGs suggested mononeuropathy multiplex. However steroid-pulse therapy was done, left drop foot and sensory-palsy was observed. Plasma exchanges (PEs) was done immediately. He was also taken intra-venous cyclophosphamide-pulse therapy (IVCY) following to 7-times PEs. After these treatments, his neuropathic manifestations improved. Cutaneous PN (CPA) and PN is the same necrotizing vasculitis. However, CPA only has vasculopathic manifestations limited within the skin lesions. In this case, we had a case in patient with long-term CPA, progressed to PN with mononeuropathy multiplex after streptococcal infection, which is very rare and valuable case.

### P3-204

#### **Gastrointestinal symptoms and associated factors in patients with Sjögren's syndrome**

Naoto Azuma<sup>1</sup>, Yoshinori Katada<sup>2</sup>, Sachie Kitano<sup>1</sup>, Aki Nishioka<sup>1</sup>, Masahiro Sekiguchi<sup>1</sup>, Masayasu Kitano<sup>1</sup>, Kiyoshi Matsui<sup>1</sup>, Hajime Sano<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan, <sup>2</sup>Sakai City Hospital, Sakai, Japan

Conflict of interest: None

[Objectives] To assess gastrointestinal symptoms and the relationship between the severity of their symptoms and clinical findings in patients with Sjögren's syndrome (SS). [Methods] 18 primary SS patients were enrolled. Gastrointestinal symptoms were evaluated using self-administered questionnaires, the Gastrointestinal Symptom Rating Scale (GSRS). The GSRS subscales consisted of reflux, abdominal pain, indigestion, diarrhea and constipation. The association among salivary flow rate, EGF levels (using an enzyme-linked immunosorbent assay), the severity of intraoral manifestations (using the Oral Health Impact Profile (OHIP)-14) and medical treatment regimen were analyzed. [Results] The total GSRS score was higher in the SS patients compared with the general population (1.94 vs 1.53). Severity increased in all GSRS subscales. Although there were five patients (28%) who complained of gastrointestinal symptoms at the time of medical examination, nine patients (50%) had mild, moderate and severe gastrointestinal symptoms in the GSRS. The higher the total salivary EGF output became, the severer the gastrointestinal symptoms was. [Conclusion] SS patients show increased severity of gastrointestinal symptoms. The severity of gastrointestinal symptoms seems to be related to saliva quality.

### P3-205

#### Ten years follow-up of salivary gland functions and submandibular gland ultrasonography in patients with Sjögren's syndrome

Naoki Hashimoto<sup>1</sup>, Masayasu Kitano<sup>3</sup>, Hajime Sano<sup>3</sup>, Tsuyoshi Iwasaki<sup>4</sup>, Takenori Hashimoto<sup>1</sup>

<sup>1</sup>Hashimoto Rheumatology Clinic, <sup>2</sup>OMM Medical Center, <sup>3</sup>Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, <sup>4</sup>Department of Pharmacotherapy, Hyogo University of Health Sciences

Conflict of interest: None

[Objectives] The aim of this study was to examine association between salivary gland functions and submandibular gland (SG) ultrasonography (US) findings during long-term follow-up in patients with Sjögren's syndrome (SS). [Methods] Fifty-six SS patients were studied. SGUS findings were evaluated by US staging and PD grading score. [Results] The mean durations of follow-up period were 10.1 years. Whole salivary flow (WSF) was decreased during follow-up ( $p < 0.01$ ). The difference of SG size was decreased in anti-SS-A antibodies (SS-A) negative than in SS-A positive SS patients ( $-38.66$  vs  $12.45\text{mm}^2$ ,  $p < 0.05$ ). In contrast, the differences of SG size and blood flow rate determined by PD grading score were significantly decreased in anti-centromere antibodies (ACA) positive than in ACA negative SS patients. Logistic-regression analysis demonstrated close association between decreased WSF and factors such as age ( $< 60$  years old), SG size ( $\geq 200\text{mm}^2$ ) and positive ACA. [Conclusion] The present study demonstrated that WSF was decreased in early stage SS patients ( $< 60$  years old, SG size  $\geq 200\text{mm}^2$ ) during 10 years follow-up. In addition, positive ACA was associated with decreased WSF, SG size and blood flow. SGUS may be a useful tool for follow-up ACA-positive early stage SS patients.

### P3-206

#### Diagnostic usefulness of the diagnostic guideline for pediatric Sjögren's syndrome in patients with Sjögren's syndrome regarded as early stage of disease

Kumiko Akiya<sup>1</sup>, Yuki Takane<sup>1</sup>, Harumi Kuda<sup>1</sup>, Mari Ushikubo<sup>1</sup>, Hisaji Oshima<sup>1</sup>, Minako Tomiita<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, National Hospital Organization Tokyo Medical Center, Tokyo, Japan, <sup>2</sup>Department of Allergy and Rheumatology, Chiba Children's Hospital, Chiba, Japan

Conflict of interest: None

[Background] Recently immunosuppressive therapy such as mizoribine or rituximab was reported to be valid to Sjögren's Syndrome (SS), and it is expected that the effectiveness of therapy increases by the early diagnosis and the early treatment as the rheumatoid arthritis therapeutic. [Methods] The subjects of this study were 347 patients who underwent examination for the diagnosis of the Sjögren's syndrome in the Tokyo

Medical Center. We studied 87 cases who were negative in Gum/Saxon test [Results] Using the clinical diagnosis as the gold standard, the diagnostic guideline for pediatric SS had a sensitivity of 94.9 % and a specificity of 81.8%. [Conclusion] The diagnostic guideline for pediatric Sjögren's syndrome showed high sensitivity compared to the Japanese criteria.

### P3-207

#### Lung involvement in primary Sjögren's syndrome

Eriko Ishioka<sup>1</sup>, Katsuya Suzuki<sup>1</sup>, Naoshi Nishina<sup>1</sup>, Kunihiro Yamaoka<sup>1</sup>, Tsutomu Takeuchi<sup>1</sup>

<sup>1</sup>Division of Rheumatology and Clinical Immunology, Keio University School of Medicine, Tokyo, Japan, <sup>2</sup>Division of Pulmonary Medicine, Department of Medicine, Keio University School of Medicine, Tokyo, Japan, <sup>3</sup>Department of Radiology, Keio University School of Medicine, Tokyo, Japan

Conflict of interest: None

[Objectives] Lung involvement is a major systemic manifestation of primary Sjögren's syndrome (pSS). The prevalence in pSS is various (9-75 %) and details are unclear. Aim of this study is to clarify the prevalence and types from case series as possible as precisely. [Methods] Total 296 patients with pSS diagnosed according to the 1999 revised Japanese Ministry of Health criteria for the diagnosis of SS between January 2012 and September 2014 at our division were enrolled after exclusion of secondary SS. All patients were underwent chest imaging either X-ray or computed tomography. [Results] Lung involvement was observed in 69 patients (24.1%, mean age; 68.9 years, all were female); interstitial lung disease ( $n=18$ , 6.0%), cystic lesion ( $n=4$ , 1.3%), chronic airway lesion ( $n=12$ , 4.0%), nontuberculous mycobacterial infection ( $n=9$ , 3.0%; definitive diagnosis cases,  $n=4$ , 1.3%), lung cancer ( $n=3$ , 1.0%), malignant lymphoma ( $n=3$ , 1.0%), others such as nodules and thickening of pleura ( $n=19$ , 6.4%). [Conclusion] Lung involvement on imaging test was observed in one-fourth cases with pSS. From the aspect of both not a few positive cases and its varieties including malignancies, chest-screening test at the point of diagnosis and in appropriate intervals should be considered in pSS patients.

### P3-208

#### Sleep disturbance in primary sjogren syndrome

Kousaku Tsuda, Goichi Kageyama, Yuiko Kamei, Ikuko Naka, Takaichi Okano, Soshi Takahashi, Miwa Nishida, Kengo Akashi, Keisuke Nishimura, Sho Sendo, Yo Ueda, Akira Onishi, Yoshinori Kogata, Jun Saegusa, Akio Morinobu  
Rheumatology and Clinical Immunology, Kobe University Graduate School of Medicine

Conflict of interest: None

[Objectives] Sleep disturbance is a frequent feature in sjogren syndrome (SS). The aim of this study was to evaluate subjective sleep quality and the related factors. [Methods] We examined 41 primary SS patients (all were women). In all patients, subjective sleep quality were assessed by Pittsburg Sleep Quality Index (PSQI). As the related factors, depression, accompanying subjective symptom of SS, symptom of sleep apnea were assessed by Patient Health Questionnaire-9 (PHQ-9), EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI), Epworth Sleepiness Scale (ESS). [Results] PSQI levels were  $9.23 \pm 5.1$ . Approximately 66% of them had a diagnosis of sleep disorder (PSQI $>5$ ). PSQI was significantly correlated with PHQ-9 ( $p=0.001611$ ), but not with ESSPRI and ESS. [Conclusion] It was suggested that depression might be intimately associated with decline of sleep quality in questionnaires in SS.

### P3-209

#### Siblings suspected of having Sjögren's syndrome with some other autoimmune diseases

Minako Tomiita<sup>1,2</sup>, Akiko Yamaide<sup>1</sup>, Akira Hoshioka<sup>1</sup>, Naoki Shimojo<sup>2</sup>

<sup>1</sup>Department of Allergy and Rheumatology, Chiba Children's Hospital, Chiba, Japan, <sup>2</sup>Department of Pediatrics, Graduate School of Medicine, Chiba University, Chiba, Japan

Conflict of interest: None

In this report, we describe two siblings with Hashimoto disease, autoimmune hypertriglyceridemia and suspected Sjögren's syndrome (SS) who were born from the mother with systemic lupus erythematosus (SLE) and SS. Case 1: The anti-nuclear antibody was positive at age one, and recurrent parotid glands and submandibular glands swelling and hypertriglyceridemia appeared from the age of 2. The anti-nuclear antibody increased to 320 times at the age of 3.6, at the same time, she developed Hashimoto disease. The serum triglyceride decreased in parallel with the titer of the antinuclear antibody. Case 2: He is the younger brother of case 1. His antinuclear antibody was positive at age 1, but it disappeared when he was 1.6 years old. Dental caries have been increasing and he has been drinking a lot of water since he was 2 years old. The antinuclear antibody changed to positive again when he was 4 years old, at the same time, he developed Hashimoto disease and hypertriglyceridemia. They are suspected of having SS and autoimmune hypertriglyceridemia caused by the anti LPL antibody. Clinical significance: Their clinical courses are suggestive of progression of autoimmune diseases.

### P3-210

#### Three Cases of Sjögren's Syndrome with Mediastinal Malignant Lymphoma

Yuki Takane, Harumi Kuda, Mari Ushikubo, Kumiko Akiya, Hisaji Oshima

Department of Internal Medicine, National Hospital Organization Tokyo Medical Center, Tokyo, Japan

Conflict of interest: None

[Case 1] A 45-year-old woman with SjS underwent CT scan which showed an enlarged thymus. She had thymectomy, and the histology revealed atypical B cells forming lymphoepithelial lesions (LEL) to make a diagnosis of MALT lymphoma. She has had no relapse after the thymectomy. [Case 2] A 30-year-old woman with SjS had CT scan, and it showed a cystic tumor in the anterior mediastinum. The thymectomy was performed, and a pathological diagnosis was thymic MALT lymphoma. The patient received infusions of Rituximab, but aseptic meningitis developed and led to the cessation of therapy. [Case 3] A 79-year-old woman with SjS had mediastinal lymphadenopathy which was pointed out on CT scan. Thoracoscopic mediastinal lymph node biopsy led to the diagnosis of DLBCL. R-CHOP was started, but one year later she developed relapse in the lingual tonsil and cervical lymph node recurrence. Radiation therapy made them disappear, but about one year later, relapses in the breast and the lingula of lung were found. They disappeared after salvage therapy. [Discussion] Thymic MALT lymphoma is rare in lymphoma, only about 60 cases having been reported in the literature. Many of them are complicated with SjS. DLBCL shows an aggressive clinical course, and careful follow-up is important.

### P3-211

#### A case of Lymphocytic interstitial pneumonia in primary Sjögren's syndrome

Koji Kobayashi, Atsumu Osada, Atsushi Ihata, Shohei Nagaoka

Department of Rheumatology, Yokohama Minami Kyousai Hospital, Yokohama, Japan

Conflict of interest: None

A 61-year-old woman was presented to our hospital complaining of dry mouth in March 2007. She was diagnosed with primary Sjögren's syndrome (SS) based on positive Saxon test and Schirmer's test, severe hypofunction of salivary gland scintigraphy finding, antinuclear antibody (ANA) (speckled pattern, 1:5120), positive SS-A/Ro antibody and SSB/La antibody. In August 2014, chest computed tomography scan demonstrates areas of ground-glass in both lower lung fields without her symptoms of cough and dyspnea. Transbronchial lung biopsy was performed and biopsy specimens revealed diffuse and massive lymphocytic and plasmacytic infiltrate in the alveolar septa without interlobular septa and vascular wall, which was compatible with lymphocytic interstitial pneumonia (LIP). There was no evidence of malignancy in the biopsy specimens. According to pathological findings, we diagnosed with LIP asso-

ciated with primary SS. Her symptoms and images of pulmonary lesion have been improved markedly with 0.5mg/kg/day of the prednisolone. The occurrence of LIP associated with primary SS is rare and we report this case with literal consideration.

### P3-212

#### A case of idiopathic intracranial hypertension occurring in Sjögren's syndrome

Kiichi Unoda, Youhei Fujiki, Daisuke Wakura, Reiko Wakura, Shuzo Yoshida, Takuya Kotani, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa

Osaka Medical College, Osaka, Japan

Conflict of interest: None

[Objectives] To report a case of idiopathic intracranial hypertension developed in association with Sjögren's syndrome. [Methods] Case report of a 20-year-old woman. She gave a slight fever and headache and progression to abnormal vision. In ophthalmology, she was pointed out papilledema and visual field disturbance, and admitted to our hospital. BMI was 21.8kg/m<sup>2</sup>. JCS0. There were no nuchal rigidity, no motor weakness, no sensory impairment. Edematous changes in the optic nerve sheath in the brain MRI, but no barain parenchyma lesions, and no abnormality was found in the MRA and MRV. In cerebrospinal fluid examination, initial pressure was 28cmH<sub>2</sub>O, cell number and protein were normal. Metabolic endocrine function was normal. Therefore we diagnosed with idiopathic intracranial hypertension. Anti SS-A and SS-B antibody positive. Greenspan grade4 in salivary gland biopsy, and we diagnosed her with Sjögren's syndrome. [Results] From after the cerebrospinal fluid examination, headache and papilledema was to regress. [Conclusion] Idiopathic intracranial hypertension is seen in the women of childbearing age, the cause is associated with drugs and obesity, but is unknown exactly. Sjögren's syndrome should be considered as one of the conditions that indicate the idiopathic intracranial hypertension.

### P3-213

#### Successful treatment with cyclosporine for autoimmune neutropenia associated with Sjogren syndrome

Tatsuki Matsumoto, Kosuke Inoue, Yoshinori Taniguchi, Kazu Ode, Yoshiko Shimamura, Koji Ogata, Shuichi Nakayama, Makoto Tsugita, Taro Horino, Yoshio Terada

Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi University

Conflict of interest: None

[Case] A 61 year-old man has presented intermittent fever for one year. He was referred to our hospital for investigation of intermittent fever of unknown origin. The laboratory investigations demonstrated neutropenia and positive anti-nuclear antibody, SS-A and SS-B antibodies. Despite the administration of G-CSF, lasting neutropenia less than 1500/ $\mu$ l was revealed. The investigations after admission demonstrated that reduced lacrimation and lymphocyte infiltration around the dust of salivary gland from his lip biopsy specimen, indicating Sjogren syndrome (SjS). Furthermore, we diagnosed as autoimmune neutropenia (AIN) associated with SjS due to positive level of anti-neutrophil antibody. Treatment with oral PSL 40mg daily was initiated, however, neutropenia was not improved. Therefore, additional treatment with cyclosporine (CyA) was initiated, and neutropenia improved. [Conclusion] When neutropenia is revealed in patients with autoimmune diseases, to investigate serum level of anti-neutrophil antibody plays a pivotal role. It is common to complicate AIN in lupus, but it's rare in SjS. This case suggested successful treatment with combined treatments with PSL and CyA for AIN associated with SjS, and we discuss about possible therapy for AIN with literatures.

### P3-214

#### A case of Sjogren's syndrome with remarkable pancytopenia

Toshiharu Sasaki<sup>1</sup>, Yonsu Son<sup>1,2</sup>, Nobuyasu Ishii<sup>2</sup>, Minoru Shigesaka<sup>2</sup>, Saki Tsujimoto<sup>1,2</sup>, Akihiro Tanaka<sup>1,2</sup>, Keiko Shimamoto<sup>1,2</sup>, Tohru Nishizawa<sup>2</sup>, Hideki Amuro<sup>2</sup>, Yoshio Ozaki<sup>1,2</sup>, Shosaku Nomura<sup>2</sup>

<sup>1</sup>Department of Rheumatology, Kansai Medical University Hirakata Hospital, Hirakata City, Japan, <sup>2</sup>First Department of Internal Medicine, Kansai Medical University, Hirakata City, Japan

Conflict of interest: None

Case: A 52 year-old female who has been treated as Hashimoto's disease complained continual fever. She was pointed out leukocytopenia, thrombocytopenia and positivity of ANA (1:1280), and referred to our hospital. Her blood examination showed 500/ $\mu$ L of WBC and 80,000/ $\mu$ L of platelet. Besides fever, she had oligo-arthritis, dry eye and dryness of mouth. The close investigation result indicated she had the ectocornea injury, positivity of anti SS-A, SS-B antibodies and gum-test. Result of salivary scintigraphy was compatible with Sjogren's syndrome. Since her cytopenia was serious, we treated her with 0.5 mg/kg/day of prednisolone. After beginning of treatment, she was also diagnosed as MDS based on bone marrow biopsy. In addition to that, she had anti-granulocyte antibody. She had a satisfactory response to treatment with glucocorticoid. Although It is unknown what her cytopenia was caused by, glucocorticoid seems to be useful for her pathophysiology. Occasionally autoantibody production in MDS patients are experienced. The pathogenic association between these autoantibodies production and the onset of the autoimmune disease still needs more data to be clarified.

### P3-215

#### **A boy of macrophage activated syndrome (MAS) in systemic juvenile idiopathic arthritis (sJIA), at first diagnosed as Kawasaki disease**

Kazuya Hamada, Noriko Kinjo

Department of Child Health and Welfare, Faculty of Medicine, University of the Ryukyus, Okinawa, Japan

Conflict of interest: None

[Introduction] Macrophage activation syndrome (MAS) is a systemic inflammatory condition based on hypercytokinemia complicated with the sJIA. Early diagnosis could be improved the prognosis. We report the one boy of MAS in sJIA, at first diagnosed as Kawasaki disease. [Case] 18 months old boy. He was onset with fever and erythema, diagnosed with incomplete Kawasaki disease at the 6th day (4/6 symptoms). He wasn't respond to IVIG, infliximab, and plasma exchange therapy, and the results of the cytokine profile, recognized the increase IL-6 and significant increase in IL-18 levels. We diagnosed with sJIA, which merged the MAS. We started steroid, and cyclosporin (CyA) therapy. Because of remittent fever, elevation of ferritin and IL-18 has been sustained, in the 47-49th day, underwent a blood purification therapy. After that we underwent mPSL pulse therapy and underwent Lipo-DEX and CyA intravenous continuous infusion with post-therapy. [Conclusion] Significant increase in IL-18 level was useful for differentiating sJIA (MAS) from incomplete Kawasaki disease. Blood purification therapy was effective in the cytokine removal. The increases in IL-18 and ferritin levels were correlated with the disease activity, and were useful in determining therapeutic effect.

### P3-216

#### **A case of childhood-onset Sjogren syndrome with peripheral neuropathy**

Nami Okamoto<sup>1</sup>, Kosuke Shabana<sup>1</sup>, Takuji Murata<sup>1</sup>, Hiroshi Tamai<sup>1</sup>, Kiichi Unoda<sup>2</sup>

<sup>1</sup>Department of Pediatrics, Osaka Medical College, Osaka, Japan, <sup>2</sup>Neurology, Department of Internal Medicine I, Osaka Medical College, Osaka, Japan

Conflict of interest: None

[Objectives] Sjogren syndrome (SjS) sometimes accompanies with peripheral neuropathy, but pediatric case seems to be very rare. Childhood-onset SjS (cSjS) is an important differential diagnosis for pediatric patient of rheumatic disease with melalgia. [Methods] We inspect 15-year-old girl with fatigue, fever, ambulatory arthralgia and edema on limbs. [Results] She complained the above matters and visited clinic. Because of hyper-gammaglobulinemia and positive RF, they diagnosed her as juvenile idiopathic arthritis and introduced to previous hospital.

Arthritis wasn't found by physical and image examination. Meloxicam, methotrexate and prednisolone were administered, but her symptom didn't change. Adalimumab nor tocilizumab did work and she was transferred to our hospital. We found edema on limbs, allodynia and attenuation of deep tendon reflex. As a result of close inspection, she was diagnosed as cSjS with autosomal and sensory neuropathy. We administered intravenous immunoglobulin, pregabalin and mizoribine, then pain and edema improved. For remained fatigue and asomnia, we started tacrolimus, etizolam, droxidopa and supportive therapy. [Conclusion] We insist that pediatric patient who is suspicious to has rheumatic disease must be investigated whether they has cSjS.

### P3-217

#### **A case of autoimmune hepatitis associated with juvenile idiopathic arthritis and Sjögren syndrome**

Toru Igarashi<sup>1,2</sup>, Takeshi Matsuyama<sup>2</sup>, Shingo Yamanishi<sup>1</sup>, Yujiro Tanabe<sup>1</sup>, Hikaru Takeshita<sup>1</sup>, Yusuke Ozaki<sup>1</sup>, Takako Miyamae<sup>2</sup>, Yasuhiko Itoh<sup>1</sup>

<sup>1</sup>Nippon Medical School, <sup>2</sup>Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: None

A 16-year-old female case of autoimmune hepatitis associated with juvenile idiopathic arthritis and Sjögren syndrome was reported. She was admitted to our hospital because of abnormal liver function with complaints of arthralgia. Polyarthritis and dryness of the mouth were evident. Anti-nuclear antibody and anti-LKM-1 antibody were positive. Anti-smooth muscle antibody was negative. Histology of the biopsied-liver tissue revealed interface hepatitis with rosette formation of hepatocytes. The level of serum transaminase improved after steroid therapy.

### P3-218

#### **A case of juvenile idiopathic arthritis with juvenile systemic lupus erythematosus**

Juri Tsukahara<sup>1</sup>, Koji Harada<sup>1</sup>, Yuto Kasahara<sup>1</sup>, Koichi Sumida<sup>1</sup>, Yukinari Yamaguchi<sup>1</sup>, Yasuhiro Akai<sup>2</sup>

<sup>1</sup>Department of Nephrology and Rheumatology, Rakuwakai Otowa Hospital, <sup>2</sup>Center for Rheumatic Disease, Nara Medical University Hospital

Conflict of interest: None

**Case report:** A 14 year-old boy was referred with arthritis in the both knees and all metatarsophalangeal and metacarpophalangeal joints lasting for more than 2 months. Because the contrast-enhanced MRI revealed synovitis with erosive and destructive bone changes in the carpal bones, he was diagnosed as juvenile idiopathic arthritis (JIA). As rheumatoid factor (RF) was negative, he was classified as RF negative polyarthritis according to the ILAR classification. Meanwhile, he had proteinuria, hemolytic anemia, hypocomplementemia and positive for ANA titer of 1: 80 (speckled, cytoplasmic) and for double-stranded DNA antibody, and he was associated with juvenile systemic lupus erythematosus (SLE). Prednisolone 30 mg/day and azathiopurine 50 mg/day were started with satisfactory improvement of arthritis, proteinuria, and hemolytic anemia. **Summary:** Simultaneous development of JIA and SLE is very rare. We report this case with literature review for the association between JIA and juvenile SLE.

### P3-219

#### **An intractable case with overlap syndrome with mixed connective tissue disease (MCTD) and scleroderma (SSc)**

Yusuke Ozaki, Shingo Yamanishi, Yujiro Tanabe, Hikaru Takeshita, Toru Igarashi, Yasuhiko Itoh  
Nippon Medical School Hospital, Tokyo, Japan

Conflict of interest: None

[Introduction] In juvenile onset MCTD, SLE-like symptoms are more frequent; on the other hand, SSc-like symptoms are less frequent than in the adult form of the disease. We present an intractable case of a girl, diagnosed as MCTD by typical symptoms, but later diagnosed as overlap syndrome with MCTD and SSc by scleroderma and positive anti



centromere Ab. [Case] A 15-year-old girl had photosensitivity at 8 years of age, Raynaud's phenomenon and myositis at 12. She was diagnosed as having MCTD by these symptoms in conjunction with high level of anti U1-RNP Ab. mPSL pulse therapy was effective, but PSL tapering was difficult. Additional IVCY therapy led to remission once. At this time, she suffered from a digit ulcer, which was improved by bosentan treatment. When IVCY therapy interval became every three months, PSL tapering induced recurrence. After that, scleroderma and anti-centromere Ab were found. Because of fulfilled diagnostic criteria of SSc, she was diagnosed of overlap syndrome with MCTD and SSc. A combination therapy of mPSL pulse, PE, and IVCY lead to remission again. Recently, her maintenance therapy is PSL, MZR, and IVCY. We present the case, which is very rare with discussion with respect to the pathophysiology based on cytokine profiles

### P3-220

#### A case of infant onset Systemic Sclerosis

Kenichi Yamaguchi<sup>1</sup>, Satoshi Fujikawa<sup>1,2</sup>, Hiroyuki Baba<sup>1</sup>, Shunya Kaneshita<sup>1</sup>, Chisun Min<sup>1</sup>, Masei Suda<sup>1</sup>, Yuri Ohara<sup>1</sup>, Ryo Rokutanda<sup>1</sup>, Hisanori Shimizu<sup>1</sup>, Yukio Matsui<sup>1</sup>, Tokutaro Tsuda<sup>1</sup>, Mitsumasa Kishimoto<sup>1</sup>, Masato Okada<sup>1</sup>

<sup>1</sup>Immuno-Rheumatology Center, St. Luke's International Hospital, <sup>2</sup>Fujikawa Pediatric Clinic

Conflict of interest: None

[Background] Onset of systemic sclerosis (SSc) in childhood is uncommon. Furthermore we have very limited clinical information about infant-onset SSc. We report a 3 years old girl with diffuse cutaneous SSc (dcSSc) who had developed Raynaud's phenomenon in infancy. [Case] The patient was a 3 years old girl suffered from Raynaud's phenomenon which was exacerbated in winter and even in summer in air-conditioned room from infancy. Dermatologist had diagnosed her as chilblains. She had developed fever of unknown origin with antinuclear antibody-positive at age of 1. She visited our hospital for purpose of receiving detail inspection. She had developed disseminated erythema, edematous change in the finger and toe and nailfold capillaries change with positive anti-Scl-70 antibody (over 850 U/mL). She had no organ complications, such as pulmonary arterial hypertension and interstitial pneumonia. We diagnosed her as dcSSc using the ACR/EULAR criteria for the classification of SSc. The frequency of Raynaud phenomenon was clearly reduced after we improved living environment to avoid cold exposure. [Conclusion] We summarize clinical characteristics of child-onset SSc, and discuss about treatment of infant-onset SSc especially about the importance of environmental improvement.

### P3-221

#### Occipital lobe epilepsy secondary to posterior reversible encephalopathy syndrome in a pediatric patient with Takayasu arteritis

Utako Kaneko

Department of Pediatrics, Niigata University, Niigata, Japan

Conflict of interest: None

We report the case of 12-year-old girl with Takayasu arteritis presented with seizures as clinical manifestations of posterior reversible encephalopathy syndrome (PRES) due to renovascular hypertension complicated with occipital lobe epilepsy. She attended emergency department with generalised tonic-clonic seizures, prolonged unconsciousness, and severe hypertension. Magnetic resonance imaging (MRI) findings were suggestive of PRES. CT angiographic findings showed stenosis of bilateral renal artery, superior mesenteric artery, and celiac artery. She was diagnosed as having Takayasu arteritis and treated with corticosteroids and Ca-channel blocker. She responded well to the treatment. After two weeks, she developed visual disturbance and partial seizure with secondary generalization. An EEG displayed a pattern of focal spike in left occipital regions. She was diagnosed as having status occipital lobe epilepsy, and treated with carbamazepine and free from seizure. The ADC map showed a vasogenic edema pattern in the right occipital region and cytotoxic pattern in the focal left occipital region. MRA showed partial vasoconstriction in left posterior cerebral artery. This case suggested that cerebral vasoconstriction due to prolonged hypertension could underlie PRES and epilepsy.

### P3-222

#### Clinical Analysis of Hypertrophic Pachymeningitis

Risa Wakiya, Hiroki Ozaki, Hiromi Shimada, Shusaku Nakashima, Yohei Takeuchi, Miharū Izumikawa, Tomohiro Kameda, Kentaro Susaki, Hiroaki Dobashi

Department of Internal Medicine, Division of Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University, Kagawa, Japan

Conflict of interest: None

[Objectives] Hypertrophic pachymeningitis (HP) is a rare, chronic, inflammatory disorder of the dura mater. Recently, imaging diagnosis is developing and the number of HP case is increasing. However there is no criteria about diagnosis and treatment. [Methods] We investigated the clinical features and treatment results 6 patients (M/F: 2/4) with HP diagnosed and treated between 2000 and 2014. [Results] The average age at diagnosis was 43.7 y.o. (18-73) The initial symptom of headache was recognized in 5 cases, eye pain in 3 cases, fever in 2 cases, low vision in 2 cases, double vision in 2 cases, nausea in 1 case and tinnitus in 1 case. 4 cases have an underlying disease and Sjögren's syndrome in 2 cases, mixed connective tissue disease in 1 case, granulomatosis with polyangiitis in 1 case. The initial treatment is only prednisolone (PSL) in 2 cases, methylprednisolone-pulse in 3 cases and combination of PSL and immunosuppressive agent in 2 cases. 2 cases were flared and improved with addition of immunosuppressive agent. [Conclusion] HP induces various symptoms and corticosteroids are effective as an initial treatment. We reported the clinical features and treatment results of HP including bibliographical consideration.

### P3-223

#### One case report of TAFRO syndrome with Sjögren syndrome

Masashi Fukuta, Kotaro Kumano, Masaki Hiraguri, Takao Yanagisawa Narita Red Cross Hospital

Conflict of interest: None

A 79 years old man was diagnosed as primary Sjögren syndrome (SS) with interstitial pneumonia (IP), and followed it up in outpatient department once in several months. In the beginning of March, 2014, the patient came to hospital with thrombocytopenia, anasarca, fever, renal dysfunction, anemia, coagulation disorder, and C-reactive protein elevation. After admission, various kinds of antibiotics and anticoagulant therapies were administered, which was invalid. After  $\gamma$  globulin massive dose therapy and glucocorticoid therapy was commenced, CRP began to decrease in around two weeks and was normalized on the 21st day. Platelet counts increased around 30<sup>th</sup> day. We are tapering steroid since then and it has not recurred for seven months as far. [Clinical significance] Pathology and etiology of TAFRO syndrome is unclear. There are no specific autoantibody and clinical manifestations. It is possible that TAFRO syndrome is one of the autoimmune diseases which could react well to the glucocorticoid, since autoimmune diseases are often consistent. Our case was consistent with Sjögren's syndrome as well. It is necessary to accumulate the case of TAFRO syndromes..

### P3-224

#### A case of Kikuchi-Fujimoto disease presenting with aseptic meningitis and polyarthritis

Toshimasa Shimizu<sup>1</sup>, Remi Sumiyoshi<sup>1</sup>, Fumiaki Nonaka<sup>1</sup>, Atsushi Kawakami<sup>2</sup>, Katsumi Eguchi<sup>1</sup>

<sup>1</sup>Department of Rheumatology and Metabolism, Sasebo City General Hospital, Nagasaki, Japan, <sup>2</sup>First Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan

Conflict of interest: None

[Objective] We present a case of Kikuchi-Fujimoto disease (KFD) presenting with aseptic meningitis and polyarthritis. [Case] A 39 y/o female presented bilateral cervical lymphadenopathy and fever. Treatment with an antibiotic drug was not effective. After several days, she presented severe headache. Her cerebrospinal fluid cultures showed pleocytosis but the culture were negative for bacteria. We diagnosed aseptic meningi-

tis and started conservative management. Her symptoms of headache dissipated. However, lymphadenopathy and fever remained and polyarthritis appeared. Serology for antinuclear antibodies, rheumatoid factor, anticitrullinated protein antibody and several virus were negative. A computed tomography scan showed lymphadenopathy of left cervical and supraclavicular, and mild splenomegaly. Cervical lymph node biopsy showed immunoblasts with lymphohistiocytic infiltration and nonspecific necrotic material, consistent with KFD. Her symptoms dissipated with nonsteroidal anti-inflammatory drug therapy after two months. [Conclusion] KFD is a self-limited disease characterized by regional lymphadenopathy. Aseptic meningitis and polyarthritis are rare extranodal manifestations of KFD. Regardless, KFD included in the differential diagnosis for meningitis and polyarthritis.

### P3-225

#### Malabsorption syndrome associated with chronic thrombotic microangiopathy in a patient with scleroderma and Sjögren's syndrome

Shinya Tamechika, Shinji Maeda, Taio Naniwa, Akio Niimi  
Department of Respiratory Medicine, Allergy and Clinical Immunology, Nagoya City University School Medical Sciences

Conflict of interest: None

A 51-year-old woman was admitted to our hospital because of congestive heart failure. She had had diarrhea from her childhood period. A few months before admission, peripheral edema, exertional dyspnea, weight gain, and low-grade fever had developed and worsened. On admission, she also had sclerodactyly, proteinuria, hypoalbuminemia, and pancytopenia. Diuretics and antihypertensive agents improved heart failure, but couldn't improve diarrhea and edema. Positive results of anti-centromere and anti-Ro antibodies, and results of skin and lip biopsies led us to diagnoses of limited cutaneous scleroderma and Sjögren's syndrome. Malabsorption syndrome were diagnosed by many fat droplets in stool; hypoalbuminemia and hypocholesterolemia; leakage of radio-labeled albumin into gastrointestinal tract demonstrated by <sup>99m</sup>Tc-HSA scintigraphy. Also, platelet microthrombi weren't found in the biopsy of the duodenum and ileum and skin, but presence of pancytopenia and fragmented erythrocytes and undetectable serum haptoglobin lead us to the diagnosis of thrombotic microangiopathy. High-dose glucocorticoid improved diarrhea, pancytopenia, proteinuria, hypoalbuminemia, but induced severe gastrointestinal hypomotility. We will discuss this rare association of these manifestations with literature.

### P3-226

#### Four cases that needed the differential diagnosis of erythema nodosum-like rash

Kana Tanji<sup>1</sup>, Takuya Hirai<sup>1</sup>, Keigo Ikeda<sup>1</sup>, Shinji Morimoto<sup>1</sup>, Yoshinari Takasaki<sup>2</sup>, Iwao Sekigawa<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Juntendo University Urayasu Hospital, Chiba, Japan, <sup>2</sup>Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan

Conflict of interest: None

<Case1>A 38-year-old woman appeared to fever, myalgia, muscle weakness and erythema nodosum (EN)-like rash on both lower limbs. Mediastinum lymphadenopathy was seen in CT scan. Malignant lymphoma and others were suspected. The lymph node biopsy led to a diagnosis of tuberculosis. <Case2>A 31-year-old woman appeared to fever, polyarthritis and EN-like rash on right lower limb. Finally, the elevation of ASO and ASK led to a diagnosis of hemolytic streptococcus infection. <Case3>A 35-year-old woman appeared to fever and EN-like rash on sole of right foot. Aortitis syndrome was made a diagnosis based on thickening of the aortic wall in CT/MRI and abnormal accumulation to an aortic wall in PET-CT. <Case4>A 34-year-old woman appeared to fever, arthralgia and multiple-relapsed EN-like rash on left femur after antibiotics treatment. Both the characteristic of the symptom and the histological finding from rash led to be considered Weber-Christian disease or panniculitis with Sjögren's syndrome. In most of cases showed EN-like rash, Behcet disease is most common diagnosis for rheumatologist in Japan. However, EN-like rash is known as a sign complicated with various diseases and differential diagnosis is important. We will report four cases

with bibliographic considerations.

### P3-227

#### A case of renal sarcoidosis relapsed with the cutaneous and neurological manifestations

Yuto Kasahara<sup>1</sup>, Koji Harada<sup>1</sup>, Juri Tsukahara<sup>1</sup>, Koichi Sumida<sup>1</sup>, Yukinari Yamaguchi<sup>1</sup>, Yasuhiro Akai<sup>2</sup>

<sup>1</sup>Rakuwakai Otowa Hospital, Kyoto, Japan, <sup>2</sup>Center for Rheumatic Disease, Nara Medical University Hospital, Nara, Japan

Conflict of interest: None

**Case report:** A 73 year-old woman with renal sarcoidosis was admitted for hypercalcemia, subcutaneous nodule, and numbness in the both lower limbs. Three years before admission acute kidney injury developed. Because renal biopsy showed the noncaseating granulomatous interstitial nephritis, she was diagnosed as renal sarcoidosis. Glucocorticoid was started with satisfactory improvement of renal function and discontinued 12 months later. Six months after discontinuation of corticosteroid renal function was aggravated again, and the steroid treatment had been re-instituted for 6 months. One week before admission she noticed subcutaneous nodule and feeling of numbness in the both lower limbs. On admission she had hypercalcemia and elevation of serum angiotensin-converting enzyme. Since nerve conduction velocity showed the demyelinating polyneuropathy and skin biopsy revealed the noncaseating granuloma, relapse of sarcoidosis was confirmed. Methylprednisolone pulse therapy followed by 25 mg/day oral prednisolone was started with the improvement of serum calcium, skin and neurological involvement.

**Summary:** Because the extrarenal organ manifestations may emerge later in the patients with renal sarcoidosis, adequate glucocorticoid dose and prolonged treatment prevent to relapse.

### P3-228

#### A case of sarcoidosis which developed malignant lymphoma with pulmonary infiltration

Minako Hakamata, Takayasu Suzuka, Shuzo Yoshida, Yoshihiro Hirai, Takeshi Shoda, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa  
Department of Internal Medicine(I), Osaka Medical College, Takatsuki City, Osaka, Japan

Conflict of interest: None

A 76-year-old male with bilateral hilar lymphadenopathy was diagnosed with pulmonary sarcoidosis in 2007. In 2010, he was diagnosed with cardiac sarcoidosis because of left ventricular systolic dysfunction, right bundle branch block, and endomyocardial biopsy specimen. He was treated with prednisolone (PSL) 1 mg/kg every other day, anti-arrhythmic drugs and cardiac resynchronization therapy defibrillator because of ventricular tachycardia. In 2011, methotrexate (MTX) 8 mg/week was started because of dyspnea. In May 2014, he complained of fever and dyspnea. A chest computed tomography showed bilateral diffuse granular shadows and infiltrative shadows in bilateral lower lobes, and hemophagocytosis was complicated. Methyl PSL pulse therapy was performed with no response. A lymph node biopsy specimen confirmed diffuse large B-cell lymphoma. MTX was discontinued, and chemotherapy (rituximab, cyclophosphamide, doxorubicin, etoposide, PSL) was performed with a good response. Sarcoidosis is often complicated with malignant lymphoma, which is diagnosed by splenic and lymph node involvement in most cases. In sarcoidosis patients, lymphoma with pulmonary infiltration is rare but an important complication distinguished from pulmonary sarcoidosis.

### P3-229

#### A case of autoimmune pure white cell aplasia complicated with cystic thymoma

Hideyuki Okada, Yoshihiro Uno, Mami Iida  
Gifu Prefectural General Medicine Center, Gifu, Japan

Conflict of interest: None

78-year-old woman presented to our hospital with fever, lip aphthous ulcer and polyarthralgia. A blood count demonstrated severe neutropenia

with a white blood cell count of 900 / $\mu$ L and absolute neutrophil percentage of 0 %. HGB 9.4 g/dL, PLT  $27.4 \times 10^4$  / $\mu$ L, RET 9 %, CRP 20.23 mg/dL, LDH 96 IU/L, TSH 0.25  $\mu$ IU/mL, FT3 1.74 pg/mL, FT4 1.36 ng/dL, ANA (Homogeneous pattern)  $\times 80$ , and MPO-ANCA was positive. PR3-ANCA, RF, Anti-cyclic citrullinated peptide antibody (ACPA), anti-dsDNA antibody, anti-Sm antibody and anti-acetylcholine receptor antibody were all negative. Bone marrow biopsy revealed granulocytic aplasia. Computed tomography showed a cystic thymoma. She was diagnosed with pure white cell aplasia associated with cystic thymoma. Although she was treated with antibiotic and antifungal agents, she did not remit. She received two times of steroid pulse therapy and once steroid mini-pulse therapy, subsequently, she was treated by oral prednisolone and tacrolimus. Then, she was fully recovered with a white blood cell count of 9000 / $\mu$ L and neutrophil percentage of 85 %. Autoimmune pure white cell aplasia is a very rare. But etiology is not unclear. Therefore, elucidation of the etiology is expected in the near future.

### P3-230

#### A case of rheumatoid arthritis complicated with gastric GIST with liver metastasis

Hiroo Hashimoto<sup>1</sup>, Kiichi Komoto<sup>1</sup>, Kazuhiko Moriwaki<sup>1</sup>, Takehide Mitogawa<sup>2</sup>, Fumio Otsuka<sup>3</sup>

<sup>1</sup>Internal Medicine of Innoshima General Hospital, <sup>2</sup>Internal Medicine of Onomichi Municipal Hospital, <sup>3</sup>Department of General Medicine, Okayama University Hospital

Conflict of interest: None

A 64-year-old female RA patient was administered MTX 12.5 mg/week and PSL 4 mg/day. She had cough since May in 201x. Chest CT incidentally demonstrated the gastric tumor. The laboratory data: CRP 0.34 mg/dl and RF 56 U/ml. Abdominal CT demonstrated gastric tumor (size 6.5 cm) with enhancement effect. GIF showed the submucosal tumor and the biopsy specimen was revealed to be Group 1. On July in 201x, partial gastrectomy was performed. The specimen showed spindle and epithelioid cells with positive c-kit and CD34, and the diagnosis was GIST (gastrointestinal stromal tumor). On March in 201x+2, since liver metastasis was found, the partial liver resection was performed. On April in 201x+2, MTX was ceased and treatments with PSL: 4 mg/day and Imatinib: 400 mg/day were started. Imatinib was ceased due to eruptions on May in 201x+2. On September in 201x+2, Tacrolimus: 1 mg/day and PSL: 5~6 mg/day were administered. On July in 201x+3, the liver metastasis was relapsed, and Sunitinib: 25~37.5 mg/day was then administered instead of Tacrolimus. After Sunitinib (4 cools) treatment, the liver metastasis gradually became small and arthralgia disappeared. We discuss about the immunosuppressive and biological agents for the RA patients complicated with the malignancy.

### P3-231

#### Palmoplantar pustulosis conjoined with uncontrolled rheumatoid arthritis (RA). Case report

Chinatsu Azuma<sup>1</sup>, Hidehiro Horizon<sup>2</sup>, Fuminori Kanaya<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery University of Ryukyus, <sup>2</sup>JINON Orthopedic Surgery Clinic

Conflict of interest: None

Multiple joints pain started at 43 y-o. Methotrexate (MTX) therapy was started under the diagnosis of RA. Infliximab (IFX) was started after 6 months and continued for 2years. He stopped IFX therapy by economic reasons and MTX was increased to 16mg/W for 1.5 years. Patient showed low disease activity. (DAS28-ESR: 2.8). He stopped medication after 6 months, and his disease activity got worse (CRP: 2.8, ESR: 78, DAS28ESR: 4.9). At 51 y-o, he could not walk because of joints deformity, pain and swelling, and showed high disease activity (CRP: 10.8, ESR: 98, DAS28-ESR: 5.9). He had neither infection nor malignancy, but suddenly developed multiple pustules on bilateral palms and bilateral plantae. Bacterial examination was negative, and skin biopsy revealed palmoplantar pustulosis. Tocilizumab therapy was started. ESR and CRP became lower, but joints swelling were unchanged (DAS28-ESR: 5.0). [Discussion] Palmoplantar pustulosis have been reported as paradoxical reaction of anti TFN- $\alpha$  antibody therapy. Since IFX was stopped 6 years

ago, the palmoplantar pustulosis of this patient occurred independently.

### P3-232

#### A case of Lymphangiomyomatosis(LAM) with RA

Junko Kawata

Kawata-Junko Clinic

Conflict of interest: None

Lymphangiomyomatosis (LAM) is a rare lung disease that results in a proliferation of smooth muscle growth throughout the lungs, resulting in the obstruction of small airways. I present the case of 64-year-old woman who has LAM with RA. [case]64-year-old woman came to our clinic because of the treatment of arthritis. She was diagnosed renal angiomyoma, operated and cured in 2004. Laboratory evaluation revealed that unremarkable findings. RF (-), ACPA (-), SS-A (-), SS-B (-), Serum amyloid protein (-), Schirmer test (-), and Saxon test (-). MRI of hands showed there are synoviocytes proliferation in PIP joints of right 3<sup>rd</sup>, 4<sup>th</sup> and left 4<sup>th</sup>, and also bone destructions. Chest X ray: reticular shadows in both lower lung fields. Chest computed tomography (CT): There are many cysts all over the lung fields. Lung biopsy: acidophilic spindle-shaped cells (+). Immuno-stain: Anti- $\alpha$ -smooth muscle actin (SMA) Antibody (Ab) (+), Anti-HMB45 Ab (-), Anti-progesterone receptor (PR) Ab (+). From criteria she was diagnosed LAM with RA. Follow-up CT showed no change last year, and RA is observed with no medication. [discussion] It was uncertain the correlation between LAM and RA. Since HMB45 Ab was negative, it should be stained by Melan-A and S-100 because of the proof of melanocyte character as a LAM.

### P3-233

#### Rituximab (RTX) was effective in treating two cases with connective tissue disease (CTD)-associated thrombotic microangiopathy (TMA)

Takayasu Kise<sup>1</sup>, Takahiro Nunokawa<sup>1</sup>, Naonori Tsuda<sup>1</sup>, Kae Onishi<sup>1</sup>, Yuji Miyoshi<sup>1</sup>, Satoshi Watanuki<sup>1</sup>, Yoshiki Nagai<sup>1</sup>, Eigo Kikuchi<sup>1</sup>, Toshioki Sawaki<sup>1</sup>, Naoto Yokogawa<sup>1</sup>, Kota Shimada<sup>1</sup>, Naofumi Chinen<sup>2</sup>, Shinji Sato<sup>2</sup>, Yasuo Suzuki<sup>2</sup>, Shoji Sugii<sup>1</sup>

<sup>1</sup>Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Tokai University, School of Medicine, Isehara, Japan

Conflict of interest: None

[Case 1]78 year-old man had exhibited shortness of breath, dry cough, Raynaud's phenomenon, finger erythema, hardness to swallow, fever, arthralgia, weakness and high CK level. He was admitted to our hospital in September 2013. He had Gottron's sign, Mechanic's hand, weakness of proximal muscle, anti-EJ antibody, interstitial pneumonia, inflammatory myositis. He was diagnosed with anti-ARS antibody syndrome. After steroid was started, he complicated with TMA. Plasma exchange (PE) was performed but he wasn't improved. Adding on RTX, myositis and TMA were improved. [Case 2]16-year-old woman was admitted in June 2014 because of skin eruption, proteinuria, hematuria, bleeding tendency, malaise, arthralgia, malar rash, oral ulcer, visual loss. She also had pancytopenia, antinuclear antibody and anti-ds-DNA antibody. She was diagnosed with SLE. Since she also complicated with retinopathy and nephritis, steroid and intravenous cyclophosphamide were started. Afterward, she also complicated with alveolar hemorrhage, reversible encephalopathy syndrome and TMA. We had performed PE, her condition hadn't been improved. We added on RTX and her condition was improved. [Clinical significance] CTD-associated TMA has lower response of PE and poorer prognosis than TTP. RTX may improve its prognosis.

### P3-234

#### The effect of teriparatide on skeletal muscle

Yuki Kishida, Miho Nakanishi, Keisuke Hagihara

Department of Kampo Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

Conflict of interest: None

[Objectives] Various treatment methods have been proposed for reductions in motor function in patients with rheumatoid arthritis (RA); however, reductions in muscle quality and mass remain great issue to be resolved, especially elder people. Teriparatide is a recombinant form of human parathyroid hormone and used in the treatment of RA sufferer complicated osteoporosis. We investigated the effect of teriparatide on skeletal muscle which also related to calcium metabolism. [Methods] The skeletal muscles were investigated in senescence-accelerated mice. Teriparatide was administered three times a week. These muscles were subjected to HE staining and immunostaining. Gene expression was assessed using Western blotting. Vehicle control was identically experimental approach. [Results] Teriparatide improved grip strength and reduction of fast-skeletal muscle. Although these mice had abnormalities in the expression of TNF $\alpha$  and PGC-1, they all improved following teriparatide administration. [Conclusion] These findings suggest both that teriparatide alters grip strength and the ratio of fast and slow skeletal muscle via improvement in mitochondrial function and suppression of inflammation.

### P3-235

#### **A case of podocytic infolding glomerulopathy with Rheumatoid Arthritis**

Tamaki Sasaki, Naoki Kashihara

Department of Nephrology and Hypertension, Kawasaki Medical School

Conflict of interest: None

Podocytic infolding glomerulopathy (PIG) has been proposed as a new disease entity. PIG is characterized by specific changes to the thickened glomerular basement membrane (GBM), including microspheres, microtubular structures, and podocytic infolding. Only a small number of cases of PIG have been reported. The clinical features and pathogenesis of this condition are still unclear. The patient was a 6X-year-old woman who was diagnosed with RA at the age of 5X- and had been medicated with DMARDs. She was admitted into our hospital, and underwent renal biopsy because of the proteinuria. Light microscopic findings revealed a minor glomerular abnormality, but under a higher magnification, after periodic acid methenamine silver staining, a bubbling appearance in the glomerular basement membrane (GBM) was observed. An electron microscopic examination revealed microspheres in the GBM, which were sparse but global. The patient was diagnosed as having PIG with RA. The mechanisms underlying the development of PIG in RA are unknown, but the cause of these morphological changes in the GBM might be associated with autoimmune disorders. These findings contribute to elucidate the pathogenesis of the GBM lesions.

### P3-236

#### **A case of systemic senile amyloidosis with the first symptom of carpal tunnel syndrome**

Akira Yoshida, Tamao Nakashita, Akira Jibatake, Kotaro Matsumoto, Yuto Hamada, Shinji Motojima  
Kameda Medical Center, Rheumatology and Allergy, Kamogawa, Japan

Conflict of interest: None

Senile systemic amyloidosis (SSA) is a disease which shows deposition of wild-type transthyretin (TTR) in many organs resulting finally in arrhythmia and cardiac failure in elderly people. It has been reported that in SSA carpal tunnel syndrome (CTS) may precedes the emergence of cardiac symptoms for several years. We present a case of SSA whose first symptom was CTS. The patient is a 67 year-old man who had been treated in the department of spinal surgery because of lumbar spinal canal stenosis since February 2012. He noticed numbness on right 1-3 fingers in January 2013. CTS was suspected from the findings such as ring finger splitting, positive Tinell's sign, and atrophy of abductor pollicis brevis muscle. The diagnosis was defined based on the findings of nerve conduction study. The open canal decompression surgery was done in July 2014. Pathological examination revealed amyloid deposition on transverse carpal ligament, and the patient was referred to our department. Immunohistochemical staining showed deposition of TTR on the ligament, and SSA was strongly suspected. Because familial amyloid polyneuropathy with mutant TTR deposition cannot be completely ruled out, gene analysis is under investigation. In conclusions, SSA should be taken into

consideration as a cause of CTS.

### P3-237

#### **The efficacy of tocilizumab in 2 patients with recurrent renal amyloidosis after the discontinuation of tocilizumab due to adverse effects**

Hiroaki Tamura, Takumi Matsumoto, Takao Katsuragawa  
Kin-ikyo-chuo Hospital, Sapporo, Japan

Conflict of interest: None

We report two patients with renal amyloidosis which progressed after the discontinuation of tocilizumab (TCZ) due to adverse effects in whom renal dysfunction was improved again by the reintroduction of TCZ. TCZ appears to have an ability to inhibit the progression of renal dysfunction of amyloid A (AA) amyloidosis complicating active RA. A 71-year-old female was diagnosed with RA 35 years ago and a 68-year-old female was 48 years ago. The former was diagnosed with AA amyloidosis by renal biopsy in 2013 and the latter by gastro-duodenal mucosal biopsy in 2009. Their clinical symptom and renal dysfunction were once improved by the introduction of TCZ treatment, but were exacerbated again due to the discontinuation of TCZ with adverse events (itching, pyogenic arthritis). Because the adverse events were settled, TCZ was administered again to each patient. After several months proteinuria had disappeared and the concentration of serum creatinine recovered to each baseline level.

### P3-238

#### **A case of rheumatoid arthritis developing with nephrotic syndrome during treatment with etanercept**

Yuki Hara<sup>1</sup>, Ayako Nishino<sup>1</sup>, Shin-ya Kawashiri<sup>1,2</sup>, Sosuke Tsuji<sup>1</sup>, Masataka Umeda<sup>1</sup>, Shoichi Fukui<sup>1</sup>, Takahisa Suzuki<sup>1</sup>, Yoshikazu Nakashima<sup>1</sup>, Yoshiro Horai<sup>1</sup>, Yasuko Hirai<sup>1</sup>, Tomohiro Koga<sup>1</sup>, Naoki Iwamoto<sup>1</sup>, Kunihiko Ichinose<sup>1</sup>, Mami Tamai<sup>1</sup>, Hideki Nakamura<sup>1</sup>, Tomoki Origuchi<sup>3</sup>, Atsushi Kawakami<sup>1</sup>

<sup>1</sup>Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, <sup>2</sup>Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, <sup>3</sup>Department of Rehabilitation Sciences, Nagasaki University Graduate School of Biomedical Sciences

Conflict of interest: None

A 66 years-old female developed rheumatoid arthritis (RA) and treated with methotrexate (MTX) in May 2010. Etanercept (ETN) was introduced because of refractory to MTX in Jun 2011. Although ETN was switched to adaribmab (ADA) in Jun 2013 because of worsening of her disease activity, she did not response to ADA. ETN was restarted in Sep 2013. Joint destruction gradually progressed. In Jun 2014, she admitted to our hospital for severe disability. She was complicated with atlanto-axial subluxation (AAS) which was adaptive to surgical treatment, and nephrotic syndrome (urinary protein 24g/gCr) which was suspected to be classified as minimal change nephrotic syndrome or membranous nephropathy. Because drug-induced nephrotic syndrome was suspected, ETN was discontinued and she was treated with steroid pulse therapy (mPSL 500mg) and following oral prednisolone 20 mg/day. A proteinuria immediately disappeared. Tocilizumab was introduced after laminectomy for AAS, and her disease activity improved. Biologic agents are unlikely to cause renal dysfunction. However, some RA patients complicated with nephrotic syndrome during treatment with TNF inhibitors were previously reported. In all the patients, nephrotic syndrome improved by discontinuation of TNF inhibitors and steroid treatment.

### P3-239

#### **[Case report] 41 years old man, CTEPH is found due to be worsening finger ulcers**

Kenji Yoshida, Kazuhiko Higashioka, Kensuke Oryoji, Kazuo Kamada, Shinichi Mizuki, Eisuke Yokota  
Institute of Rheumatology Center, Matsuyama Red Cross Hospital, Matsuyama, Japan

Conflict of interest: None

**[Case Report]** 41 years old man. **[CC]** cold sense with fingers He developed lupus nephritis in 2003, had treatment with steroids and IVCY. Anti-RNP-antibody and Antiphospholipid antibody in the blood test was high. And he developed a pulmonary embolism, he was diagnosed as SLE/APS. In May 2014, ulcer appeared on the right middle finger. Then extension of hilm pulmonis was in chest X-ray examination, and TR-PG was high (90mmHg) in Echocardiography. We diagnosed him CTEPH (Chronic Thromboembolic Pulmonary Hypertension) because of Right heart catheterization (PAH: 53mmHg), lung perfusion scintigraphy, and pulmonary artery angiography. He was treated with BPA (Balloon Pulmonary Angioplasty) in July 2014. **[discussion]** Anti-RNP-antibody or anti-Centromere-antibody positive patients is high risk of pulmonary hypertension (PH) generally, and APS patients sometimes develop CTEPH after pulmonary embolism. In this case, though he was nothing of difficulty in breathing, we suspected pulmonary hypertension from ulcer on the finger. High risk patients of PH should be suspicious of PH when they had exacerbation of peripheral circulation (Raynaud phenomenon, ulcer of finger, and so on).

### **P3-240**

#### **Safety of tacrolimus in elderly patients with rheumatoid arthritis**

Takuro Ozaki<sup>1</sup>, Shuzo Yoshida<sup>2</sup>, Takeshi Shoda<sup>2</sup>, Takuya Kotani<sup>2</sup>, Tohru Takeuchi<sup>2</sup>, Shigeki Makino<sup>2</sup>, Toshiaki Hanafusa<sup>2</sup>

<sup>1</sup>Arisawa General Hospital, <sup>2</sup>First Department of Internal Medicine, Osaka Medical College

Conflict of interest: None

**[Objectives]** To evaluate the safety of tacrolimus in elderly patients with autoimmune disease, including rheumatoid arthritis. **[Methods]** We were targeted 15 patients using tacrolimus in our hospital. Two cases were excluded because of maintenance dialysis. We examined for the incidence of hospitalization due to infectious disease and the glomerular filtration rate (GFR) after tacrolimus treatment in the elderly (over 65 years old). **[Results]** Rheumatoid arthritis is 11 cases, dermatomyositis, interstitial pneumonia, scleroderma and sarcoidosis were each for one case. The average of tacrolimus was 1.77±0.53 mg/day. Decrease of GFR was seen in nine cases. There were no difference in the rate of change of GFR between elderly patients and non-elderly patients. There were no difference in the rate of hospitalization due to infection between elderly patients and non-elderly patients. **[Conclusion]** The use of tacrolimus for elderly suffering from autoimmune disease is well tolerated.

### **P3-241**

#### **A case of 22-years-old female, diagnosed systemic lupus erythematosus, had small fiber neuropathy**

Hiroko Uesugi<sup>1</sup>, Shinichiro Tsunoda<sup>2</sup>, Momo Maruoka<sup>2</sup>

<sup>1</sup>Onsazaidan osakahu saiseikai noe Hospital, <sup>2</sup>Hyogo College of Medicine

Conflict of interest: None

Since 18 years old, she had Raynaud's phenomenon, anti-nuclear antibody anti-RNP antibody and several episodes of non-septic meningitis. She had been treated with steroid hormone. When she was 22 years old, she was suffered from continuous high fever and cough and admitted. She also had liver damage, pancytopenia and positivity of anti-ds-DNA antibody, and diagnosed as SLE. High dose steroid, steroid pulse therapy, ciclosporin and IVIg did not reduce fever. Suddenly, severe pains began in bilateral lower and upper-limbs. After 3 courses of plasma exchange and opium therapy, she showed improvement in fever, cough, liver damage and pancytopenia but continued opium therapy against severe pains. Skin biopsy was performed. The density of the small nerve fibers was decreased. The severe pains were thought to be a symptom of small fiber neuropathy.

### **P3-242**

#### **A case of the intractable rheumatoid pleural effusion that tried control with plural biological preparation**

Takao Kiboshi<sup>1</sup>, Koji Nagai<sup>1</sup>, Junichi Konma<sup>2</sup>, Masakazu Sugino<sup>1</sup>

<sup>1</sup>Aino Hospital, <sup>2</sup>Department of Internal Medicine (1), Osaka Medical

College

Conflict of interest: None

A patient of the rheumatoid arthritis morbid about 40 years. He was given bucillamine (200 mg/day) in 2008. It became the hospitalization in previous medicine by a diagnosis of the pleurisy in December, 2012, and got a diagnosis of the rheumatoid pleural effusion. After starting methotrexate (MTX) 4mg/week and adalimumab (ADA) 40mg/2 week in January, 2013, the disease activity decreased, and pleural effusion decreased. But, pleural effusion increased in October, and he performed surgery for intussusception due to rectal cancer for the same time. After that he canceled MTX and ADA, and started salazosulfapyridine (1000 mg/day). Pleural effusion increased in December, and after starting prednisolone (20 mg/day) as treatment reinforcement, it became the tendency to decrease, but it increased again. Disease activity of RA is high in joint ultrasonography, so abatacept and tocilizumab were began, and disease activity of RA decreased, but pleural effusion was not improved and switched to certolizumab from November. I experienced a case of the intractable rheumatoid pleural effusion that tried control with plural biological preparation. A lot of any questions about disorder of rheumatoid pleural effusion, and we reported pleural profile in this case and reviewed the literatures.

### **P3-243**

#### **Acute mediastinitis by esophageal perforation during treatment with tocilizumab in patient with rheumatoid arthritis (RA)**

Daisuke Murakami, Koichiro Taguchi, Kei Fujioka, Tatsuo Ishizuka

Ceter of General Internal Medicine and Rheumatology, Gifu Municipal Hospital

Conflict of interest: None

70-year-old woman had been treated RA with MTX (6mg) and PSL (2.5mg) for 24years, and tocilizumab (162mg) for 2 years. On the May 3, 200x, She noticed neck and chest pain. On May 4 and 5 she admitted to our emergency department. Although rheumatic changes in cervical spine were observed with X-ray, no other abnormalities were noted, she returned home. On May 6 high CRP (23mg/dl) and high WBC (13100/ $\mu$ l) were pointed in an orthopedic doctor. Severe infection was suspected and she was sent by ambulance to our hospital. Chest CT showed wall thickening in the upper esophagus, pericardial effusion and pleural effusion. Therefore, acute mediastinitis and pleurisy were suspected caused by esophageal perforation. After confirmation of exudative pleural effusion, MEPM+CLDM administration started. Although mild redness was observed in the middle esophagus on EGD, no certain perforation and diverticulum were found. On May 19 chest CT showed infiltration shadow in the right lower lobe. Since *S.pyogenes* was detected form blood culture, MEPM was switched to CTRX. However, the infiltrate tend to enlarge, and organizing pneumonia was diagnosed by TBLB on May 30. June 4, CLDM was finished because the pleural effusion decreased. After the infiltrate improved, administration of CTRX was ended.

### **P3-244**

#### **A case of abrupt onset rheumatoid arthritis (RA) complicated with rheumatoid vasculitis (RV)**

Yuko Kashiara, Masao Tamura, Makoto Terada

Itami City Hospital

Conflict of interest: None

**[Case]** A 63-year-old man who had not any special concerns in his medical history. He was admitted to our hospital at September 2014, because of fever, cough and multiple arthralgia. He had sever inflammatory reaction (high levels of CRP and ESR, neutrophillia). Chest and abdominal CT showed left upper lung consolidation and random GGO, and multiple small renal infarction. So, he was temporarily diagnosed as septic embolus with pneumonia and received multiple antibiotics. But antibacterial therapy did not improve his inflammatory reaction and CT findings. That is why we investigated a cause of inflammation precisely. He was presented with multiple symmetrical synovitis and serum ACPA positive. Therefore, he was diagnosed as having RA according to ACR/EULAR

diagnostic criteria. Furthermore, his serum complement level was very low (CH50 and C4 were decreased as <5U/ml and 11.5mg/dl respectively) and his pathological findings with TBLB revealed angitis of small vessels. Finally, we diagnosed him as RV complicated RA and started to treat with high-dose prednisolone which resulted in the improvement of symptoms and abnormal findings. We report here a rare case of RV that showed abrupt onset and sepsis-like findings.

### P3-245

#### Regional medical cooperation for treatment of rheumatoid arthritis in respiratory and liver disease fields

Eiichiro Watanabe<sup>1</sup>, Miho Tsujimura<sup>2</sup>, Toshiharu Shirai<sup>1</sup>

<sup>1</sup>Unit of Orthopedic, Fuji Orthopedic Hospital, Shizuoka, Japan, <sup>2</sup>Regional Medical liaison office, Fuji Orthopedic Hospital, Shizuoka, Japan

Conflict of interest: None

[Objectives] Screening for respiratory diseases and previous hepatitis B virus (HBV) infection is essential before introducing immunosuppressants. As our hospital has no respiratory and liver disease specialists, we cooperate with external specialists. We also conduct directly observed therapy (DOTS) conferences in conjunction with a public health center for latent tuberculosis infection (LTBI) cases. We surveyed regional medical cooperation in the respiratory and liver disease fields for our rheumatology outpatient practice. [Methods] Among patients with connective tissue disease (April 2013–October 2014), we studied 158 requiring medical specialist consultations. [Results] Cases requiring such consultations numbered 221 and 36, respectively. There were 9 DOTS conferences and 26 subjects. Major respiratory diseases included interstitial pneumonia, chronic bronchitis, and LTBI. There were 29 cases with HBV infected. Isoniazid was given to 27 patients, Entecavir to 5. Methotrexate was also given to 81 and 21 patients of the respiratory and hepatology departments, respectively, and biological products to 69 and 7. [Conclusion] This study revealed that regional medical cooperation allows guideline-based medical practice in hospitals without respiratory and liver disease specialists.

### P3-246

#### The occurrence of iatrogenic tuberculosis diseases in a national general hospital

Norihiko Yamaguchi<sup>1,2</sup>, Kiyokazu Yoshinoya<sup>2</sup>, Sadayoshi Yoshinoya<sup>3</sup>

<sup>1</sup>Japan Mutual Aid Association of Public School Teachers Kinki Central Hospital Respiratory Medicine, Itami, Japan, <sup>2</sup>Department of Respiratory, National Hospital Organization Osaka-minami Medical Center, <sup>3</sup>Sennan-Shinke Clinic

Conflict of interest: None

[Objectives] The number of tuberculosis patients in our country is in the decreasing tendency. However, the active tuberculosis of iatrogenic is assumed to be an increasing tendency. [Methods] The case of active tuberculosis which was first diagnosed by the tubercle bacilli culture positivity between 2014 and 2006 was gathered. [Results] Only 2 patients had been judged to be iatrogenic tuberculosis in 4 years from 2006. There were as many as 14 patients of iatrogenic tuberculosis in 4.5 years from 2010. 4 patients developed the disease in the rheumatism department and 4 patients in the hematology department and 2 patients in the respiratory department. After 2010, the iatrogenic pneumocystis pneumonia was occurred in 21 patients in the rheumatism department and 2 patients in respiratory department. 3 patients developed the same diseases in the hematology department but none of them were iatrogenic. 5 patients developed cryptococcosis, 2 developed nocardiosis, and 2 mucormycosis in the same periods. 8 patients of them were treated in the rheumatic department. [Conclusion] It seemed that the tuberculosis control in the rheumatic department had achieved successfully by the corporate programs such as the Japanese society for tuberculosis and the Japanese respiratory society.

### P3-247

#### Measurement of Neutrophil CD64 in patients with malignancy; solid cancer vs malignant lymphoma

Akiko Komiya<sup>1</sup>, Toshihiro Matsui<sup>2</sup>, Koichiro Horie<sup>2</sup>, Hidefumi Fukuda<sup>2</sup>, Hirota Tsuno<sup>2</sup>, Kanako Iwata<sup>3</sup>, Hideki Ogihara<sup>2</sup>, Tatsuoh Ikenaka<sup>4</sup>, Misato Kawakami<sup>2</sup>, Atsushi Hashimoto<sup>2</sup>, Hiroshi Furukawa<sup>3</sup>, Shigeto Tohma<sup>3</sup>

<sup>1</sup>Department of Clinical Laboratory, Sagami National Hospital, National Hospital Organization, Kanagawa, Japan, <sup>2</sup>Department of Rheumatology, Sagami National Hospital, National Hospital Organization, Kanagawa, Japan, <sup>3</sup>Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, National Hospital Organization, Kanagawa, Japan, <sup>4</sup>Department of Rehabilitation, Sagami National Hospital, National Hospital Organization, Kanagawa, Japan

Conflict of interest: None

[Objectives] Although recent studies have reported the clinical utility of measurement of neutrophil CD64 expression as an infection marker, we have sometimes observed that neutrophil CD64 is significantly upregulated in patients despite the absence of infection, especially so in patients with malignant lymphoma. The aim of this study is to evaluate the utility of neutrophil CD64 in patients with cancer, especially the diagnostic role in malignant lymphoma. [Methods] We measured neutrophil CD64 from patients diagnosed with malignancy during the follow up period in our hospital before treatment by flow cytometry. The cut-off value for CD64 detection was 2000 molecules/cell. [Results] Neutrophils from 17 patients with malignant lymphoma expressed significantly high levels of CD64 (mean ± SEM) (9831 ± 2243 molecules/cell) to those from 61 patients with solid cancer (1066 ± 63.7 molecules/cell) ( $p < 0.001$ ). [Conclusion] The quantitative measurement of neutrophil CD64 by flow cytometry may be useful in the differential diagnosis of malignant lymphoma. Neutrophil CD64 expression is now commonly accepted as an infectious marker, but it is necessary to consider the malignant lymphoma as a possible differential diagnosis when CD64 expression on neutrophils is high in clinical situations.

### P3-248

#### A case of pyoderma gangrenosum occurring in a rheumatoid arthritis patient treated with abatacept

Seiji Yoshizawa, Keiko Oda

Department of Rheumatology, Federation of National Public Service Personnel Mutual Aid Associations, Hamanomachi Hospital

Conflict of interest: None

Here, we report a 64-year-old woman who developed pyoderma gangrenosum (PG) during treatment with abatacept for her rheumatoid arthritis (RA). She had been suffering from RA for 10 years. Her joint pains had gradually deteriorated despite of systemic treatment with corticosteroids and methotrexate. Treatment with tacrolimus, etanercept, adalimumab and infliximab showed inadequate response. So, we decided to treat with abatacept, a T-cell co-stimulation blocker. Abatacept had been effective in soothing her RA symptoms without prominent adverse effects. However, a year after the start of abatacept, accumulated red papules appeared on her right thigh and got aggravated forming an ulcer with moth-eaten appearance and red halo. The diagnosis of PG was made by the histological examination. The ulcerative lesion responded well with orally administered prednisolone. The biological agents (e.g. TNF- $\alpha$  blocker) have proven to be effective in PG. On the other hand, induction or worsening of PG has been reported in patients treated with these drugs. We experienced a case of PG occurring in a RA patient treated with abatacept. We consider that this may be a case of a paradoxical reaction caused by abatacept and discuss a possible underlying disease mechanism in the present case.

### P3-249

#### A case of the MTX-related lymphoproliferative disorder that had difficulty in differential diagnosis from cancer of maxillary antrum

Keiichi Yoshimoto, Akira Tamai

Department of Internal Medicine, Kurobe City Hospital, Kurobe, Japan

Conflict of interest: None

[Case] A 71-year-old man began to complain polyarthralgia from 2007 and was diagnosed as RA at neighbor clinic. Although he was treated with 8mg/week of Methotrexate (MTX) and 3mg/day of prednisolone (PSL), control of RA was not good. Then, addition of them, he was treated with adalimumab (ADM) at our hospital from autumn of 2013. However, the effect of ADM gradually attenuated in spite of increase of MTX to 10mg/week. So we change ADM to Etanercept (ETN) at March 2014. Although RA became to be controlled well, hypoesthesia of left head and cheek developed and his cheek gradually swelled up from June 2014. Though the findings of CT and PET suggested that he had cancer of maxillary antrum, histological findings from biopsy specimen revealed the lesion was malignant lymphoma. We stopped MTX and ETN from July, and the tumor disappeared in September of 2004. [Conclusion] MTX-related lymphoproliferative disorder (MTX-LPD) occasionally develop extra nodal lesion, including intracranially. So we have to pay attention to MTX-LPD even if tumor were not typical as a lymphoma.

### P3-250

#### **A case of rheumatoid arthritis with amyloidosis on hemodialysis, who died of gastrointestinal perforation and refractory severe infection**

Shunsuke Tsuge<sup>1</sup>, Ichiro Mizushima<sup>1</sup>, Akikatsu Nakashima<sup>1</sup>, Mitsuhiro Kawano<sup>2</sup>

<sup>1</sup>Division of Nephrology and Rheumatology, Department of Internal Medicine, Ishikawa Prefectural Central Hospital, <sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Kanazawa University Hospital

Conflict of interest: None

[Case] A 55-year old woman with rheumatoid arthritis (RA) was referred to our hospital for evaluation and treatment of heart failure and suspected arteriovenous graft infection. She had received hemodialysis (HD) for 7 years because of chronic renal failure. RA remained active even after an initiation of hemodialysis, and duodenal amyloidosis was diagnosed one year before admission. However, strong therapy such as biological agents was not initiated due to renal failure and high serum  $\beta$ -D-glucan level. After admission to our hospital, we performed HD for heart failure and removed the graft for infection. However, infectious state got worse despite administration of various antibiotics, and then duodenal ulcer was diagnosed by endoscopy (Day 19). Five days later, she developed perforation of duodenum despite fasting and intravenous injections of proton pump inhibitor, and died regardless of intensive treatment at ICU (Day33). [Conclusion] It was speculated that the complications of this case including renal failure and gastrointestinal perforation were related to systemic amyloidosis due to RA activity. Despite recent advances in treatment, amyloidosis is still one of the serious complications in patients with long-standing active RA.

### P3-251

#### **A case of RA patient of lung damage with hypereosinophilia and investigation of 32cases of hypereosinophilia**

Mayumi Kawaguchi<sup>1</sup>, Akihiko Mukai<sup>2</sup>

<sup>1</sup>Mimihara General Hospital, <sup>2</sup>Coop Osaka Hospital

Conflict of interest: None

We report a 82-year-old man who got bronchial asthma in 78y.o., and RA in 80y.o. He stopped RA treatment by himself, and soon he got brain attack and lung inflammation. He also had hypereosinophilia, eruption, so we thought he got hypereosinophilic syndrome and treated with steroid. But his lung inflammation got worse to die. Postmortem autopsy appeared he had not only interstitial pneumonia but also cytomegalovirus inclusion. Purpose; To find the better way to treat patients with hypereosinophilia Patients and Methods; We evaluated all patients from Jun 2013 to Oct 2014 whose eosinocyte ratio in peripheral white cell over 30%. Result; Total 32 patients, man 19, average 70 y.o., 29 were inpatients. Average counts of eosinocytes were 3718 (min 1517, max 13585), 7cases already died and 5case changed hospital. 18cases had kidney disease (5 was undergoing HD), 12 had bronchial asthma, 6 had drug allergy, 10 had heart failure, 10 had cancer, 11 had skin trouble, 6 had lung inflammation. 11cases was treated with steroid and all got well without this case. Fol-

lowable 18 cases without steroid, only two cases was transient and most repeated or persistent. Conclusions; Many cases with hypereosinophilia improved, on the other hand 20% of them died in a year. It is important to follow the cases with hypereosinophilia.

### P3-252

#### **A case of systemic lupus erythematosus complicated by myocarditis and ventricular fibrillation**

Eiji Suzuki, Takashi Kanno

Division of Rheumatology, Ohta-Nishinouchi Hospital

Conflict of interest: None

A 36-year-old woman was brought to our emergency room due to sudden syncope. Ulcerative colitis and autoimmune hepatitis had been diagnosed at 30 years old. She had experienced high fever, general fatigue and arthritis 2 months before admission and palpitations a few weeks earlier. Cardiopulmonary resuscitation was performed and an automated external defibrillator was used. Chest radiography showed cardiomegaly. Echocardiography showed decreased cardiac function (ejection fraction, 40%). After admission, defibrillation was performed twice for ventricular fibrillation. Beta-blockers failed to improve cardiac function, and high fever continued. Systemic lupus erythematosus (SLE) was diagnosed based on alopecia, arthritis, decreased lymphocytes, pericarditis and myocarditis seen on myocardial specimens, and a high anti-nuclear antibody titer (640'). Sjögren's syndrome was also diagnosed because of the high anti-SS-A antibody titer, along with dry eyes and xerostomia. Symptoms improved after administering prednisolone at 40 mg/day. Cardiac function gradually improved (ejection fraction, 56%). Implantation of an implantable cardioverter defibrillator was planned. Myocarditis is a rare complication of SLE, but connective tissue diseases can also cause myocarditis of unknown etiology.

### P3-253

#### **A case report of acquired hemophilia A patient with high titer factor 8 auto antibody successfully treated by DDAVP**

Sadachika Arai<sup>1</sup>, Shohei Mizuno<sup>2</sup>

<sup>1</sup>Department of Medicine, Mizuno Memorial Hospital, Tokyo, Japan,

<sup>2</sup>Department of Orthopedics, Mizuno Memorial Hospital, Tokyo, Japan

Conflict of interest: None

[Case Report] 72 year old man [Conclusion] Successful management of massive intramuscular bleeding in a hemophilia A patient with high titer anti-factor 8 auto antibody by DDAVP was reported.

### P3-254

#### **A case of nonepisodic angioedema with eosinophilia**

Jun Morikawa, Junichi Tanaka

Kitasato Institute Hospital

Conflict of interest: None

We describe a case of Japanese patient whose characteristics were consistent with non-episodic angioedema associated with eosinophilia (NEAE). 57-year-old female patient was referred to our hospital because of peripheral edema and pain persistent for a month. She was prescribed prednisolone 5mg/day by a previous doctor for bronchial asthma and chronic eosinophilic sinusitis. The chief complaints were peripheral edema and pain in the upper and lower extremities. In addition, she showed increased body weight, a feeling of weariness and eosinophilia. Fever, urticaria and elevated serum IgM were not observed. She was diagnosed as having NEAE and treated with a prednisolone 30mg/day and antiallergic drugs. These clinical features were resolved in a few weeks, and no recurrence was observed. These clinical features are often similar to those of rheumatologic disease with regard to edema and pain in a symmetric fashion. NEAE was considered to be a possible diagnosis, when peripheral edema and pain are persistent.

### P3-255

#### A Case of Refractory Fibromyalgia

Masaki Akamine, Kazunori Uehara, Norio Kusunoki, Takashi Oura  
Oura Clinic Rheumatology, Okinawa, Japan

Conflict of interest: None

**[Background]** The only medication for fibromyalgia (FM) covered by insurance is Pregabalin, and various other drugs including antidepressants are prescribed to symptomatically treat chronic pain and various neurological / psychiatric symptoms. It is very difficult to treat in chronic cases as the symptoms become complicated and resistant. **[Case]** The patient had been suffering from pantalgia, depression accompanied by repetitive self-harm and left forearm paralysis due to neurotmesis since she had a traffic accident in 2001. The patient had also been treated for borderline personality disorder at a psychiatry clinic. The patient visited 7 medical facilities one after another and came to our clinic in 2013. Although her symptoms had been considered as sequela of the accident, one of the doctors referred her to a specialist suspecting FM. **Treatment:** The patient developed symptoms 12 years ago, and started to receive various medical treatments 1 year ago. **[Result]** A concomitant use / gradual increase of pregabalin and gabapentine has relieved the patient's pain. **[Discussion]** The symptoms are a collection of heterogeneous syndromes. Differentiation and individual treatment are necessary. **[Conclusion]** It is crucial to develop a new treatment method for refractory cases.

### P3-256

#### Reasons for Long Hospital Stay in Rheumatoid Arthritis Patients: A Quantitative Study

Hisashi Terakubo<sup>1</sup>, Miyuki Matsuura<sup>1</sup>, Makoto Onishi<sup>2</sup>

<sup>1</sup>Department of Nursing, Center for Rheumatic Disease, Dohgo Spa Hospital, <sup>2</sup>Internal Medicine, Center for Rheumatic Disease, Dohgo Spa Hospital

Conflict of interest: None

**(Introduction)** With the development of biologics, treatment has shifted towards remission; however the number of elderly patients with already extensively impaired joints is increasing. **(Objective)** To examine the condition of long-hospitalized RA patients at this facility. **(Method)** We evaluated patients hospitalized for at least 6 months based on age, disease stage, functional capacity class, joint replacements, and history of treatment, and ADL. **(Results)** Of 62 patients hospitalized for at least 6 months, 84% were 75 years old. Using ADL standards, 7% of patients could move independently, 19% required a walker, and 84% required assistance to move. While 33% of patients could use the toilet independently, 67% required assistance. As part of their treatments, 81% of patients used prednisone, 33% used MTX, and 27% used biologics. Joint replacements were performed in 60% of patients, averaging 3 joint surgeries per patient. We observed cervical vertebrae disorders in 90% of patients. Average RA stage was 3.4, and average class was 3.0. Average HAQ-DI was 2.5. **(Conclusion)** Long-hospitalized patients with RA tend to be older, have a history of multiple joint replacements, and often have complicating cervical vertebral disorders. We believe that these patients require continuous, highly specialized treatment and care.

### P3-257

#### Analysis of recognition of drugs used in rheumatoid arthritis treatment

Noriko Iwata, Sayuri Sasahara, Masao Sato  
Department of Rheumatology, Matsunami General Hospital

Conflict of interest: None

**[Objectives]** The aim of this study is to evaluate whether patients recognize the kinds of drugs and the name of drugs given by their doctors. **[Methods]** We received 135 responses from the Rheumatoid arthritis (RA) patients who undergoing the drug therapy using biologics. Questions were about the name and the kinds of the drugs given by their doctor. **[Results]** Thirty-four men and 101 women enrolled in this study. Age was ranged 25 years to 88 years, average 58.8 years old. Biologics used were 27 IFX, 11 ETN, 14 ADA, 43 TCZ, 29 ABT, 7 GOL, and 4

CZP. DMARDs were used in 104 patients, PSL in 36 patients, NSAIDs in 49 patients. Fifteen patients did not know the name of the biologics used in their treatment. Average of these patients age was 67.3 years old. Of 15 patients, 14 were received the biologics injection at the hospital. **[Conclusion]** This survey revealed that there were some patients who did not recognize the efficacy and the name of drugs. It is necessary to teach about the drug information such as the effectiveness, adverse effect, and the name so on.

### P3-258

#### The knowledge and understanding of infection for patients with rheumatoid arthritis treated with biologics

Haruko Kitamura  
University Hospital, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: None

**[Objectives]** We investigate the knowledge and understanding of infection for patients with rheumatoid arthritis treated with biologic DMARDs. **[Methods]** We offered outpatient with rheumatoid arthritis interview study at our institute, and 88 patients responded. Questions of the interview study are as below; Question1 (Q1) "Is it explained you are careful about a cold and infection from the chief physician?" Question2 (Q2) "Do you know that a slight cold symptom may discontinue your biologic drug temporarily?" Question3 (Q3) "Do you know what biologic drug and the immunosuppressive drug may discontinue when you get a severe cold symptom and an operation, a big injury, drainage?". We analyzed the data in consideration of the history of biologics and self-injection. **[Results]** Q1 showed 93% of patients answered "Yes", and 33% made a reply "No" in Q2 64.8% provided an answer "No" in Q3. It didn't achieve statistical significance of the history of biologics and self-injection. **[Conclusion]** It is insufficient to understand the compromised host and they couldn't practice enough the need for discontinuation of immunosuppressive drugs. The knowledge and coping with infection was not related with the history of biologics and self-injection. We need daily instruction for infection repeatedly.

### P3-259

#### The Community Medical ICT Network service available in Nagasaki prefecture, "Ajisai Net"

Taiichiro Miyashita<sup>1</sup>, Nozomi Iwanaga<sup>2</sup>, Yasumori Izumi<sup>2</sup>, Katsumi Eguchi<sup>4</sup>, Atsushi Kawakami<sup>5</sup>, Kiyoshi Migita<sup>3</sup>

<sup>1</sup>Miyashita Rheumatology Clinic, <sup>2</sup>Rheumatology, NHO Nagasaki Medical Center, <sup>3</sup>Clinical Research Center, NHO Nagasaki Medical Center, <sup>4</sup>Sasebo Municipal Hospital, <sup>5</sup>The First Department of Medicine, Nagasaki University of Medicine

Conflict of interest: None

The Community Medical ICT Network service has been gradually spreading all over the country in Japan. The 'Ajisai Network' in Nagasaki has been one of the practical service since 2004. The most valuable service of the 'Ajisai Network' is free use of Electric Hospital Records (EHR) of many hospitals from other clinics or hospitals through internet VPN. Points of this service in rheumatologic area are summarized in three points. (1) pre-screening examination before MTX and biologics introduction (medical image cooperation), (2) double-follow system with other specialized departments in complications high-risk patients (3) real-time status check of the EHR in emergently transferred patients. In this presentation, we report availability of The Community Medical ICT Network service in rheumatologic medical care.

### P3-260

#### The development of clinical tool for rheumatoid arthritis by File-Maker

Masato Isobe, Fumihiko Sakamoto, Mihoko Henmi, Akihiro Narita, Yuko Aoki, Hisanori Takamatsu, Akemi Kitano, Takeya Ito, Akio Mitsuzaki, Jun Fukae, Megumi Matsuhashi, Masato Shimizu, Kazuhide Tanimura  
Hokkaido Medical Center for Rheumatic Diseases, Sapporo, Japan



Conflict of interest: None

[Objectives] To develop and operate clinical tool for rheumatoid arthritis (RA) by Filemaker. [Methods] We have reported the usefulness of Filemaker database (FMDB) for ultrasonography sharing patient data with preexisting medical system, and until now similarly make full use of FMDB for doctor's letters, summary documents, and various order vouchers. This time we develop and operate FMDB for joint assessment, course of RA treatment, the progress of disease activity (CDAI, SDAI, DAS28), trends list of blood biochemical test, infection history (HBV, HCV, Tuberculosis), and the 2010 ACR-EULAR classification criteria for RA. [Results] We have about 1,600 RA patients (19,000 cases total) per year, and it was able to store the medical records without gap between the practitioners by unifying the evaluation item on FMDB. Required data was indicated on one screen, and it was helpful in explanation to patients. [Conclusion] The advantage of user-made database is that medical doctors and co-medical staffs could make flexible and useful FMDB quickly by themselves, and the cost is not so high. We would like to make use of FMDB in RA consultation and statistical examination by storing more data in the future.

### P3-261

#### **A trial of support system to facilitate patients enrollment in rheumatological clinical studies**

Ayako Inamura<sup>1</sup>, Takumi Doi<sup>1</sup>, Mitsumasa Kishimoto<sup>2</sup>, Masato Okada<sup>2</sup>  
<sup>1</sup>Research Management Center, St.Luke's International Hospital, Tokyo, Japan, <sup>2</sup>Immuno-Rheumatology Center, St.Luke's International Hospital, Tokyo, Japan

Conflict of interest: None

[Objectives] The number of clinical studies of new medications for the treatment of rheumatoid arthritis and systemic lupus erythematosus has been globally increasing, as that in our institutions, i.e. 21 currently ongoing studies at Immuno-Rheumatology Center. We analyzed the efficacy of enrollment support system for physicians to select appropriate candidates for various protocols during busy outpatient service. [Methods] Our support system is consistent of four steps. First, simple tables of inclusion and exclusion criteria and simplified protocols of each study are posted on the walls of consultation rooms. Second, studies are classified based on diagnoses and separately arranged in table. Third, CRC regularly sent e-mails to physicians to notify enrolling studies and current status of fulfillment. Fourth, monthly face-to face conference of physicians and CRC was held after selection of potential candidates through Electronic Medical Record review. [Results] Supporting and reminding physicians through this system was effective to enhance the recruitment of study subjects, which increased the number of patients who benefited from the researches. [Conclusion] Our comprehensive support system for physicians was effective to facilitate enrollment of patients into clinical studies.

### P3-262

#### **A research on the factors which involve in continuous remission of polymyalgia rheumatica (PMR)**

Kentaro Chino, Akiko Shibata, Ryota Sakai, Tsuneo Kondo, Ayumi Okuyama, Hirofumi Takei, Koichi Amano  
Department of Rheumatology and Clinical Immunology Saitama Medical Center, Saitama Medical University

Conflict of interest: None

[Objectives] To examine the factors which contribute continuous remission in PMR [Methods] 20 cases from June, 2005 to May, 2009 which were not associated with temporal arteritis or malignancies. Remission is defined as negative CRP and without myalgia, for 6 months or more. There were 10 patients with continuous remission (CRG) and another 10 patients without continuous remission (nCRG). Background and clinical factors were compared in these 2 groups. [Results] The sex ratio of the 2 groups were 7/3, 9/1 respectively. Age of disease onset were 71.0 (CRG) and 68.8 (nCRG). Average CRP at treatment start were 8.30, and 6.22 mg/dl, whereas MMP-3 were 219.8, 167.2 ng/ml respectively (n.s.). The duration from the therapy start to the remission induction were 10.78,

14.78 weeks. The average PSL at treatment start were 11.1, 14.4 mg/days, and the amounts of average PSL at remission were 9.3 mg and 4.0 mg. PSL could be discontinued in 7 cases in CRG and 1 in nCRG. MTX was used in two cases in both group. Hashimoto disease and diabetes are observed as complications in CRG. 1 Hashimoto disease, and 1 renal dysfunction in nCRG. [Conclusion] Disease activity was higher and average PSL at treatment start was lower in CRG. The duration from the therapy start to the remission induction was shorter in CRG.

### P3-263

#### **Infliximab for the treatment of juvenile-onset ankylosing spondylitis**

Ryosuke Sakata<sup>1</sup>, Seiji Kanno<sup>2</sup>, Shinji Minami<sup>3</sup>, Hideto Nishi<sup>2</sup>, Erabu Miyamoto<sup>2</sup>, Yasushi Toge<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Wakayama Rosai Hospital, Wakayama, Japan, <sup>2</sup>Department of Orthopedic Surgery, Wakayama Medical University, Wakayama, Japan, <sup>3</sup>Naga Hospital, Department of orthopedic Surgery, Wakayama, Japan

Conflict of interest: None

Infliximab for the treatment of juvenile-onset ankylosing spondylitis In Japan It began to be treated with infliximab for ankylosing spondylitis from 2010. And a few reports have shown its effectiveness in the management of juvenile-onset ankylosing spondylitis (AS). Case: an HLA-B27-positive 16-year-old boy with a 7-year history of recurrent arthritis and enthesitis, which had not responded to previous treatment with NSAIDs and sulfasalazine. He also was unable to walk. Infliximab was tried at a dosage of 5mg/kg and excellently tolerated. 18 weeks after the first infusion the patient was free of pain and walked without any need of crutches. In previous reports a shorter disease duration, younger age, and a lower BASFI are predictors of a major clinical response to TNF blockers in active AS. Infliximab seems to be a promising agent for treatment of active and refractory juvenile ankylosing spondylitis.

### P3-264

#### **A case of rheumatoid arthritis in a patient with autoimmune polyglandular syndrome type 3**

Katsuyuki Kawakami<sup>1,2</sup>

<sup>1</sup>Kawakami Clinic of Internal Medicine, Kyoto, Japan, <sup>2</sup>Hirakata Kosai Hospital, Osaka, Japan

Conflict of interest: None

We report a rare case of rheumatoid arthritis in a patient with autoimmune polyglandular syndrome type 3. The patient was 71-year-old woman. In 2004, she had been diagnosed with type 1 diabetes at 61 years old. In 2007, she had been diagnosed with chronic thyroiditis at 64 years old. In 2008, she had been diagnosed with isolated adrenocorticotropic hormone deficiency at 65 years old. Considering all of these disease, she was finally diagnosed with autoimmune polyglandular syndrome type 3, and have been treated with insulin, thyroid hormone, and corticosteroid. She suffered tenderness and spindle-shaped swelling of the bilateral finger joints in August 2013, and she was introduced to our hospital in December 2013. Anti-CCP antibodies and rheumatoid factor were negative. MMP-3 (2378.4 ng/ml) and CRP (9.71 mg/ml) were strongly elevated, and wrist MRI showed synovitis and bone erosions. These findings were consistent with rheumatoid arthritis. We avoided the use of methotrexate because there was a mild interstitial pneumonia, treatment with golimumab was started in January 2014. Treatment with golimumab was discontinued because of inefficacy. We changed golimumab to tocilizumab in June 2014, this treatment was remarkably effective, and are continuing currently.

### P3-265

#### **MTX related lymphoma with saddle nose and multiple lung nodules**

Yoichiro Haji<sup>1</sup>, Yoshiro Fujita<sup>2</sup>

<sup>1</sup>Division of Rheumatology, Daido Hospital, Nagoya, Japan, <sup>2</sup>Department of Rheumatology, Chubu Rosai Hospital, Nagoya, Japan

Conflict of interest: None

[Objectives] We experienced MTX related lymphoma came with Granulomatosis with Polyangiitis like symptoms. [Methods] Case: 74 year old female [Results] PMH: She developed rheumatoid arthritis 20 years ago. She was administered MTX8mg/week. 8 months prior to admission, rash on her cheek appeared, around the same time ulcer on her nose appeared and developed to saddle nose. Then she was performed biopsy she diagnosed as "vasculitis", and administered PSL20mg/day. 5 days prior to admission, She complained anorexia. She was pointed out disturbance of consciousness and hypotensive by GP, and transferred to our hospital. With physical examination, there was saddle nose. She was pointed out multiple lung nodules and tumor like mass of liver. There was no swelling of lymph nodes. On the labo test, CRP20.7mg/dl, MPO-ANCA, PR3-ANCA were negative and IL-2R 11077 U/ml was revealed. Liver biopsy detected atypical cell with relatively large nucleous. It was CD30 (+) CD3 (-) CD15 (-) CD20 (-). We diagnosed MTX associated lymphoma. We did not perform chemotherapy because the focus gradually regressed after stopping MTX. [Conclusion] This case showed GPA symptoms like saddle nose and multiple lung nodules. Finally, we could diagnose MTX associated lymphoma with liver biopsy.

### P3-266

#### A case of diffuse large B cell lymphoma(DLBCL) in RA patient with MTX

Ayae Tanaka, Ryutaro Yamazaki, Harutsugu Okada, Satoko Arai, Takayoshi Owada, Reika Maezawa, Kazuhiro Kurasawa  
Pulmonary Medicine and Clinical Immunology, Dokkyo Medical University, Tochigi, Japan

Conflict of interest: None

The lymphoma in MTX users is defined as methotrexate related-lympho-proliferative disease (MTX-LPD), one of the important complications. We report a case of DLBCL of primary clunus in RA patient with MTX. The patient was 78-year-old male who diagnosed rheumatoid arthritis (RA) in 7 years ago and was treated with MTX 4mg and tacrolims 2.5mg, that lead him in clinical remission. He felt pain in the left foot in April in 2014. That pain was expressed that like being stinged, so called, like a neuralgia. The pain incremented day by day, and he couldn't walk and move himself. And he admissioned in May. The laboratory tests showed elevation of serum C-reactive protein and procalcitonin levels and metabolic acidosis. The images of CT and MRI showed mass around the left femora. We suspected abscess, and required to drainage for orthopedist. When the mass was opened, not discharging proid, but been curettage a little dregs. The pathological findings of this mass was diffuse large B cell lymphoma (DLBCL). He was treated with R-CHOP, and the lymphoma was diminutive. After that the pain wasn't relapsed. The cases of primary clunus malignant lymphoma were reported 36 cases. This case was rare that MTX-LPD developed at clunus, we report this add in the literature considerations.

### P3-267

#### A case of peripheral SpA occurred with monoarthritis

Yohei Watanabe<sup>1</sup>, Masahiro Kondo<sup>2</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Hamada Medical Center, Shimane, Japan, <sup>2</sup>Department of Rheumatology, Shimane University Faculty of Medicine, Shimane, Japan

Conflict of interest: None

We report a case of peripheral SpA occurred with monoarthritis of the right thumb whose imaging examination is useful in diagnosis. [Patient] 42 years old, woman. The complaints were swelling and pain of IP joint of the right thumb in May 2013. The symptom was relieved temporarily with loxoprofen, but relapsed 3 months later. The fusiform swelling and pain of the right thumb but not the red flare were developed. There were negative findings from blood (CRP, ESR, RF, and anti-CCP Ab) and joint puncture exam. The o-shaped bone erosion and corona-shaped osteophytes was revealed by the plain X-ray and CT. The development of the soft tissue and bone marrow edema was observed in MRI. We established a diagnosis of peripheral SpA. Although internal use of SASP 100mg was started, it was deficient of the curative effect. The symptom and arthritis were improved with local injection of triamcinolone. [Dis-

cussion] While the disease concept and clinical signs of peripheral SpA come to be known widely, it has turned out that it is an important disease as differential diagnosis of RA. In many cases, peripheral SpA presented polyarthritis, but there was also the case in monoarthritis like as this patient. When diagnosing monoarthritis, it is necessary to set the possibility of peripheral SpA.

### P3-268

#### A case of drug-induced myositis requiring immunosuppressive therapy due to symptom persistence even after drug discontinuation

Makoto Inoue

Inoue Hospital

Conflict of interest: None

Symptoms of drug-induced myositis usually improve following discontinuation of the offending drug. We present herein a rare case of drug-induced myositis requiring immunosuppressive therapy, and review the related literature. A 33-year-old woman developed myalgia of the left leg in May 2014 that progressed to systemic myalgia. Creatinine kinase (CK) levels were elevated and as her local doctor had prescribed HMG-CoA reductase inhibitors for hyperlipidemia in April, she was referred to our institution with chief complaints of myalgia and pyrexia due to the possibility of drug-related myositis. Pathological findings of inflammatory cell infiltration of the muscle tissue together with the myalgia and elevated CK observed on blood testing led to a diagnosis of drug-induced myositis. The HMG-CoA reductase inhibitor believed to be the offending drug was discontinued on admission and her progress was observed; however, symptoms including elevated CK levels and myalgia persisted even after one week. Prednisolone therapy and high-dose steroid therapy were administered and symptoms temporarily improved. However, the myalgia and elevated CK levels recurred and combined therapy with methotrexate was initiated, after which her status improved.

### P3-269

#### A case of apparent TAFRO syndrome variant of multicentric Castleman's disease with associated pleural effusion, ascites and thrombocytopenia

Makoto Inoue

Inoue Hospital

Conflict of interest: None

The prognosis for TAFRO syndrome, a recently identified Japanese variant of multicentric Castleman's disease is reportedly poor. We present herein a 78-year-old man with apparent TAFRO syndrome in whom a favorable outcome was achieved, and review the related literature. The patient was referred to our institution by his local doctor at the beginning of February 2014 with chief complaints of pyrexia and anasarca. Fever of 38.0–38.9°C together with physical findings of superficial lymphadenopathy and anasarca were observed. Elevated inflammatory response, thrombocytopenia, anemia, hyperphosphatasemia, low lactate dehydrogenase levels, and renal impairment were revealed on blood testing. Pleural effusion and ascites were observed on imaging. Bone marrow aspiration resulted in a dry tap while lymph node biopsy revealed pathological findings resembling Castleman's disease. The TAFRO syndrome variant of Castleman's disease was suspected and treatment with steroid pulse therapy and oral corticosteroids was initiated. However, inflammation, renal impairment, thrombocytopenia, lymphadenopathy and edema persisted and treatment with tocilizumab was started, after which his status improved.

### P3-270

#### Three cases of rheumatoid arthritis which are diagnosed by trauma of foot and ankle

Akira Maeyama<sup>1</sup>, Ichiro Yoshimura<sup>1</sup>, Hiroshi Jojima<sup>2</sup>, Tomoko Nagano<sup>1</sup>, Hitoshi Nakashima<sup>3</sup>, Katsuhisa Miyake<sup>3</sup>, Masatoshi Naito<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Faculty of Medicine, Fukuoka University, <sup>2</sup>Department of Orthopaedic Surgery, Fukuoka University Chikushi Hospital, <sup>3</sup>Division of Nephrology and Rheumatology, Department of Internal Medicine, Faculty of Medicine, Fukuoka University

Conflict of interest: None

If patient's first affected joint are foot and ankle, the diagnosis of rheumatoid arthritis is often difficult. We experienced three cases which have trauma history, therefore, we have needed long time for diagnosis. It have already passed over five months until first check. All cases complained continuous swelling and pain after trauma. We could find the exist of synovitis by MRI, and monoarthritis. We diagnosed as rheumatoid arthritis by 2010 Rheumatoid arthritis Classification Criteria and started medication. All cases are cured. If patients have trauma history, the diagnosis of rheumatoid arthritis is difficult. Therefore, we have to do blood test, if unusual continuous swelling and symptom.

## Luncheon Seminar

### LS1

#### **Efficacy of interferon-gamma release assays at evaluating the risk of latent tuberculosis infection in patients with rheumatoid arthritis**

Shogo Banno

Department of Internal Medicine, Division of Rheumatology and Nephrology, Aichi Medical University, School of Medicine, Aichi, Japan

Conflict of interest: None

RA patients treated with immunosuppressive treatment, including biologics are higher risk of progression from LTBI to active TB. We aimed to evaluate the utility of QFT-3G (QFT-GIT) and T-SPOT. TB for the screening of the risk of LTBI in Japanese RA patients. We evaluated chest HRCT findings, previous TB infection in 68 RA patients. Sixty-eight treated with MTX and/or biologics were divided into 2 groups: 33 with a past history of TB and 35 without. We estimated the efficacy of QFT-3G compared with the T-SPOT. TB concurrently measured with peripheral blood CD4 positive cells. Positive QFT-3G at cut off 0.35 and 0.1 IU/ml (intermediate range) of the past TB infection group was 21.2% and 9.1%, respectively. The sensitivity and specificity of QFT-3G for discriminating with or without past infection of TB was 30.3% and 96.9%, respectively. Positive T-SPOT. TB of the past TB was 18.1%(SFC $\geq$ 8) and 6.1%(SFC 6,7: positive intermediate). The sensitivity and specificity of T-SPOT. TB at the cut off rather than 6 SFC was 25% and 100%, respectively. The decreased CD4 positive cells (<500) was seen in 32 (47%), however the PHA mitogen response of either QFT-GIT or T-SPOT. TB assays was not decreased. The rate of indeterminate results of 4.4%(3/68) for QFT-GIT and 1.5%(1/68) for T-SPOT. TB, respectively. Comparing among immunosuppressed hosts in several studies including HIV infection, the rate of indeterminate results seems to be low. Only 1 of QFT-GIT was determined an indeterminate result, because of high negative control. The agreement of these tests was high incidence, but we considered the negative results could not be ruled out the negative past infection of TB due to the low positive rate of both testing. The specificity of both QFT-GIT and T-SPOT. TB is high for discriminating between RA patients administrated of high-dose MTX and/or biologics with a past history of TB infection and those without previous TB infection by both medical history and chest CT.

### LS2

#### **Important issues in treatment of pulmonary hypertension associated with connective tissue disease**

Sumiaki Tanaka

Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine

Conflict of interest: Yes

Recently, the therapeutic options in pulmonary hypertension (PH) have expanded markedly. Seven potent effective therapeutic drugs for pulmonary arterial hypertension (PAH) are available for use in Japan. In chronic thromboembolic pulmonary hypertension (CTEPH), balloon pulmonary arterioplasty is also being trialed, with a growing record of good therapeutic outcomes. But for this expansion of therapeutic alternatives to improve the life expectancy and QOL of PH patients, more accurate differential diagnosis of PH is needed. Other questions have also developed around PAH therapeutics. For example, how should agents be selected, combined, or switched? And how can these tasks be accomplished safely? Of course, the same needs are also crucial in treatment of PH in connective tissue disease (CTD), and the same questions have drawn interest. When we consider these issues, the characterizing features of PH in CTD that most merit consideration are not simply those of PAH, its emblematic pathology; they also include the presence of pulmonary veno-occlusive disease, the presence of PH in left heart disease or in lung disease, or additional presentation of CTEPH. Complex, concomitant pathologies of these disease states may also present. Patterns of PH presentation also depend on the type of CTD involved. Specifically, the pathologic features of PH differ in systemic sclerosis (SSc) and other CTDs. The objective in these issues surrounding treatment of PH in CTD is to make further improvements in prognosis and QOL, and the most important of these issues may be the question of where to set treat-

ment goals. Measures for achieving these goals are another issue to consider; in particular, how to use PAH therapeutics, supportive therapy, and immunosuppressant therapy in each different CTD. The pathological presentation and the living situations in individual cases are extremely diverse, and extrapolation of the evidence gathered thus far requires considerable resourcefulness.

### LS3

#### Beyond remission by Abatacept

Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: Yes

Management of rheumatoid arthritis (RA) has been greatly improved over the last 10 years. The trail is clearly recorded in IORRA cohort conducted in our Institute since 2000. Patients in remission increased from 8% in 2000 to 50% in 2013. Now, 75% of patients maintained satisfactory condition in remission or low disease activity. Increasing evidences promoted standardization of management. In 2014, JCR published the first guideline, and EULAR / ACR revised their recommendations, and all indicates the way directed toward remission. It is a global consensus to aim toward remission using 'Treat to Target' strategy. Then, if the treatment works well, and the patients is in remission, what we have to do next? We are now in the stage to consider beyond remission. Remission is not the goal but a milestone in the long lasting life of patients with disease. We should consider the strategy beyond remission. There remains many issues beyond remission, including optimization of drug dose and / or interval, prevention and management of comorbid conditions, pharmacoeconomical issues and patients perspectives. On the other hand, each biologic has unique characteristics. Abatacept only has direct action to inhibit T cell activation. Furthermore, it directly inhibits osteoclast precursor cells, B cells and macrophages, thus unlike to cytokine inhibitors, abatacept is capable to modulate wide variety of immune response. As a consequence, abatacept is shown to lower the titers of autoantibodies, thus, might induce immunological remission. In addition, safety profile of abatacept has been demonstrated in many clinical studies. Based on those notions, abatacept may have advantages as the biologic considering beyond remission. There are no such report to compare the clinical course beyond remission introduced by anti-cytokine or abatacept, but it is quite interesting approach. In this seminar, I would like to discuss the significance of abatacept by demonstrating the new findings.

### LS4

#### Drug therapy of RA from the standpoint of a new JCR guideline-application to daily clinical practice and future problem-

Yutaka Kawahito

Inflammation and Immunology, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: Yes

Recently, a realistic aim for treatment of rheumatoid arthritis (RA) should be a state of clinical remission. The low disease activity is an acceptable alternative therapeutic goal, particularly in established longstanding disease. Because we become to diagnose RA early and use seven kinds of biological DMARDs in addition to enough quantity of methotrexate (MTX). Thus a treatment strategy approaches the gradually refined an ideal form. The RA treatment guideline of JCR was published in last October, while algorithms of the treatment of the recommendation of ACR and EULAR were revised. This guideline was made using GRADE (Grading of Recommendations Assessment, Development and Evaluation) method ahead of ACR and EULAR. It was based on the sense of values and preference of patients, the balance of risk and benefit of treatments and the medical economical matter, in addition to systematic literature review and expert opinion. The treatment strategy of RA is globalized and includes many common matters, but this JCR RA treatment guideline is important. Because there is a difference of a medical system and the racial characteristic, and we have original many csDMARD in Japan. The direction for uses of MTX, steroid and other csDMARD combination therapy, the choice method of the biological DMARDs are not

still enough and these remains as examination problems. Moreover, there will be many problems in future for the maintenance of remission. How should we start, reduce and discontinue the biological or biosimilar reagents and how should we reduce drug costs thinking about personal cost and medical economic problem influenced by aging of the population and increase of medical expenses? In this seminar I present an outline about drug therapy of RA based on new JCR RA treatment guideline and clinical evidences, comparing with EULAR and ACR recommendation.

### LS5

#### Early diagnosis and management of spondyloarthritis, especially focus on AS and PsA

Mitsumasa Kishimoto

Immuno-Rheumatology Center, St Luke's International Hospital

Conflict of interest: Yes

The terms spondyloarthritis, spondyloarthropathies, and seronegative spondyloarthropathy are used to refer to a family of diseases that share a group of clinical features. The preferred term for this family of arthritis is now "spondyloarthritis" (SpA). The group includes: ankylosing spondylitis (AS), reactive arthritis (formerly Reiter's syndrome), psoriatic arthritis (PsA), Juvenile SpA, enteropathic arthritis (spondylitis/arthritis associated with inflammatory bowel disease), and undifferentiated SpA. All display a variety of symptoms and signs, but they also share many features in common, including: inflammation of axial joints (especially the sacroiliac joints), asymmetric oligoarthritis (especially of the lower extremities), dactylitis (sausage digits), and enthesitis (inflammation at sites of ligamentous or tendon attachment to bone). Additional features include genital and skin lesions, eye and bowel inflammation, an association with preceding or ongoing infectious disorders, positive family history, elevated acute phase reactants, and a strong association with the human leukocyte antigen (HLA)-B27. The clinical manifestations, diagnosis, and classification of the SpA family of disorders in adults will be reviewed here with a focus on AS and PsA. AS and PsA are a frequent, severe and anti-TNF-responsive phenotypic subtype of SpA. In agreement with the new ASAS classification criteria for axial and peripheral SpA and emerging data on TNF blockade including adalimumab in AS and PsA, these data emphasize the need for early diagnosis and its differential diagnosis, optimal treatment, and its strategies in daily practice. Finally, I will introduce new ACR AS and axial SpA management guideline.

### LS6-1

#### The best middle reliever of RA treatment: Beneficial use of tacrolimus

Atsushi Kaneko

Dept. of Orthop. Surg. And Rheumatology, Nagoya Medical Center, National Hospital Organization

Conflict of interest: None

Tacrolimus (TAC) has passed 10 years since it was approved in Japan. According to NinJa (National Database of Rheumatic Diseases by iR-net in Japan) the frequency of TAC is increasing every year, up to 10.3%. In the current data of the 1,373 cases medicated TAC, only 440 patients (32.0%) were medicated TAC monotherapy, 933 (68.0%) were taking combination therapy; MTX + TAC (n = 401), TAC + other csDMARD (n = 202), MTX + TAC + other csDMARD (n = 77), biological DMARD (BIO) + TAC (n = 145), MTX + TAC + BIO (n = 74), TAC + other csDMARD + BIO (n = 25), MTX + TAC + other csDMARD + BIO (n = 8). Although the selection of drug medication is not clear, combination therapy might be beneficial use of TAC. In this lecture, I introduce the most recent results of the Post Marketing Surveillance "Review of safety and efficacy by TAC additional combination in patients with rheumatoid arthritis of biologics effect insufficient" 172 RA patients showed insufficient effect (SDAI>3.3) with biological agent had an additional combination of TAC. The mean age was 61.9 ± 12.1, mean disease duration was 11.0 ± 8.3 year, 42.5% patients were affecting RA for more than 10 years. RF-positive was 81.0%, anti-CCP antibody was positive 86.4%, Bio naïves were 34.9%, Bio exposed were 65.1%, Concomitant MTX use was 67.4%. At 24weeks, SDAI remission or LDA rates were 58.5%, CDAI were 57.8%. The EULAR criteria of DAS28-CRP, by Yamanaka basis, Good response were 33.6%, Moderate response were 36.2%. Ad-

verse event rates were 10.5%. SAEs, herpes zoster and myocardial infarction was one case respectively. Infection; 2.3%(4cases), renal dysfunction 1.2%(2cases), cardiac dysfunction 0.6%(1case), impaired glucose tolerance 0.6%(1case). Safety had been fully secured. For patients who had insufficient effect with biologics, TAC additional combination therapy is effective and safe. TAC is "The Best Middle Reliever" of RA treatment in the future.

## LS6-2

### The use and role of tacrolimus in treatment of rheumatoid arthritis

Ayako Nakajima

Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: None

Tacrolimus is a calcineurin inhibitor, which was developed in Japan and used for rheumatoid arthritis (RA), other autoimmune diseases and transplantation. The efficacy of tacrolimus for RA was demonstrated in the placebo controlled randomized controlled trial studies and the effectiveness of tacrolimus was confirmed to the patients who were treated unsuccessfully with methotrexate (MTX) in daily practice. Recently, the results of the post marketing surveillance was disclosed and the efficacy in prevention of joint destruction in patients with early RA in a double-blind, randomized, placebo-controlled study was also demonstrated. However, how extent the effectiveness of tacrolimus in subsiding RA disease activity compared to that of biologics or MTX has not yet been executed. In daily practice, tacrolimus is supposed to be used for patients who have different background from patients who are treated with biologics or MTX, thus the double-blinded trials of tacrolimus against MTX or biologics may not be appropriate. Thus, we analyzed effectiveness of tacrolimus compared to biologics or MTX by using propensity score matched patients in the IORRA cohort. In this luncheon seminar, I would like to summarize the effectiveness of tacrolimus through literatures and present the result of our comparative study leading to proposal of the optimal use of tacrolimus.

## LS7-1

### Safety of Tofacitinib based on current findings

Kunihiro Yamaoka

Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine

Conflict of interest: Yes

Introduction of biologics have resulted in tremendous progress in treatment of rheumatoid arthritis (RA) enabling disease control in significant proportion of patients. However, there are still patients that are difficult to control disease activity. Tofacitinib is orally available and is the first JAK inhibitor approved for RA that exhibit anti-rheumatic activity by inhibiting multiple cytokine signaling pathways. Clinical studies in RA patients with diverse background have shown that efficacy can be achieved before long starting dosage and that similar with biologics. Nevertheless, the current major concerns of Tofacitinib are the incidence of malignancies and infections. Therefore, accumulated clinical trial data has been proactively analyzed to clarify the safety profile and have been reported at domestic and international meetings. Latest analysis demonstrated that incidence of infection and malignancy was comparable with existing biologics. As a matter of fact, Tofacitinib was highly effective in Japan with significantly increased incidence of herpes zoster compared to Europe and the US. As for the incidence of malignancies, lung cancer was most commonly observed in Europe and the US, whereas gastric cancer was most commonly observed in Japan. For the time being, it is not clear as to whether there is any direct relation between these adverse events and inhibition of JAK-STAT signaling. Further investigation is on going considering various possibilities, including genetic and environmental factors. In this lecture, I will focus on safety, especially on its change after approval of Tofacitinib in Japan including the latest post-marketing surveillance. I will also discuss on the tips of initiation and follow up during treatment with Tofacitinib, based on my personal experience and outline the future prospective.

## LS7-2

### Effectiveness of tofacitinib based on clinical data and our own experience

Toshihiro Matsui

Department of Rheumatology, Sagamihara National Hospital, National Hospital Organization, Kanagawa, Japan

Conflict of interest: Yes

Dramatic progress has been made in recent years in the treatment of rheumatoid arthritis (RA). Factors accounting for such achievement include establishment of clear therapeutic goals, start of aggressive treatment mainly with methotrexate (MTX) from early stages, and emergence of some highly effective biologics. Data from the National Database of Rheumatic Disease by iR-net in Japan (NinJa) show that the use of MTX and biologics is increasing year by year. According to NinJa 2013, approximately 70% of patients received MTX and approximately 25% received biologics. However, at present, only approximately 30% of all patients (half of those receiving MTX) undergo treatment with MTX alone. The remaining 70% need treatment in combination with other disease-modifying antirheumatic drugs (DMARDs) or biologics. Although seven biologics have already been launched in Japan, some patients are refractory to them, and all of the drugs are administered through parenteral routes. A new oral drug has therefore been much awaited. Tofacitinib, an oral small-molecule compound that specifically inhibits Janus kinase (JAK), an intracellular tyrosine kinase, is reported to demonstrate comparable therapeutic efficacy to biologics from the early stage of treatment. And yet, at the same time, post-marketing surveillance has been conducted to collect sufficient data on safety concerns, including herpes zoster and malignancy. In this seminar, I will present clinical trial data and also examine the effectiveness of tofacitinib based on our clinical trials and experience of its use in more than 40 patients in daily clinical practice. In addition, I will discuss the positioning of tofacitinib in RA treatment based on the selection criteria for use specified in the ACR 2015 draft recommendations for managing RA.

## LS8

### Endothelin and pulmonary hypertension: from basic science and preclinical study to clinical medicine, and future expectation

Takashi Miyauchi

Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, University of Tsukuba

Conflict of interest: None

1. Discovery of endothelin (ET), development of its antagonists and pulmonary hypertension (PH): A potent vasoconstrictor peptide, ET, was discovered in 1988 at University of Tsukuba. ET acts via activation of two receptor subtypes, ET<sub>A</sub> and ET<sub>B</sub> receptors. We firstly reported that an ET<sub>A</sub> receptor antagonist was effective in PH rats. ET antagonists (ET<sub>A</sub> selective antagonist ambrisentan, ET<sub>A</sub>/ET<sub>B</sub> non-selective antagonist bosentan) are currently used clinically in the treatment for PH patients. 2. The drugs for cGMP elevation (tadalafil, riociguat) and ET antagonists in PH: The stimulation of ET<sub>A</sub> receptors causes constriction of the vascular smooth muscle cells (VSMC), whereas the stimulation of ET<sub>B</sub> receptors on vascular endothelium produces NO release and elevation of cGMP in VSMC, and hence causes relaxation of VSMC. The phosphodiesterase type 5 (PDE5) inhibitor tadalafil and the stimulator of soluble guanylate cyclase riociguat elevate cGMP levels in VSMC, thereby causing relaxation of pulmonary vessels. In pulmonary vessels in rats, it has been reported that simultaneous application of an ET antagonist and tadalafil caused greater relaxation than each drug alone, and that intensity of relaxation was much greater in the ET<sub>A</sub> antagonist ambrisentan than in the ET<sub>A</sub>/ET<sub>B</sub> antagonists (bosentan, macitentan) (Liang et al., Hypertension 2012). In PAH patients, it was also reported that simultaneous application of ambrisentan and tadalafil showed greater effects than each drug alone (Phase IIIb/IV). In pulmonary vessels in rats, it was also reported that simultaneous application of an ET antagonist and riociguat caused greater relaxation than each drug alone, and that intensity was much greater in ambrisentan than in the ET<sub>A</sub>/ET<sub>B</sub> antagonists (bosentan, macitentan) (Liang et al., 2014). 3. Future expectation: ET antagonists will be used more widely in PAH patients, and will have further target diseases as heart failure, diabetic nephropathy, systemic hypertension, etc.

## LS9-1

### The actual use and clinical usefulness of golimumab

Shigeki Momohara

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Conflict of interest: Yes

Golimumab was launched as 6<sup>th</sup> biologic agent and as 4<sup>th</sup> anti-TNF agent in September 2011. Approximately 5,000 patients who had been administered the drug by the end of May in 2013, and we examined its profile in terms of the safety and efficacy under everyday practice. Approval dosage of this drug, MTX combination can be selected not only standard dosage 50mg but also 100mg at the time, in addition, under without MTX condition only 100mg can be selected to cover variable background of patients. Use of golimumab 50mg monotherapy is out of the approved dosage; however this administration has been selected to patients who have a high-risk background. On the other hand it could be suggested that golimumab 100mg + MTX selected relatively low risk background patients. Evidence of golimumab 100mg usage all over the world including Japan is limited; this research result is considered to be very valuable findings. Golimumab is evaluated as one of the lowest immunogenicity biologic agent, as a result we need to examine how affect the safety and efficacy data of this drug by MTX combination rate and MTX dosage. Various incidences of adverse events were separated into 4 different golimumab dosage groups. Furthermore, we analyzed the efficacy evaluation such as disease activity of transition. We would like to discuss about how to maximize the benefit-risk balance of this drug under the daily practice.

## LS9-2

### The safety profile of golimumab from the drug use-results survey

Atsushi Kawakami

Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences

Conflict of interest: Yes

After launch in 2011, the drug use-results survey of golimumab has been conducted. Registered rheumatoid arthritis patients treated with golimumab were more than 5,000 cases under real clinical condition, and data on the efficacy around safety are integrated. Patient background was mean  $62.7 \pm 13.2$  years of age, disease duration  $10.96 \pm 10.3$  years, and so on. The proportion of patients with bDMARDs use experience in the past that it is beyond the half, more than 65 years of age accounted for 49.78%. Those established background were reflected from the reason of 6<sup>th</sup> bDMARDs clinically approved in Japan. Among the safety analysis for 5,137 cases, adverse event ratio was 15.03% in total, this survey showed similar trend of other bDMARDs in the past and "infections and parasitic diseases" was the highest with 6.46%. The incidence of serious adverse event is 4.96% including the most recognized serious adverse event 0.66% "pneumonia". The results were examined using multiple logistic regression analysis for factors involved in serious infections; dysfunction of classification of rheumatoid arthritis (ClassIII + ClassIV), history-merger of respiratory disease, history-merger of renal dysfunction, those risk factors were detected. Dose of concomitant MTX, dose of golimumab, in addition, from the perspective of past bDMARDs use experience were examined under this survey. Those who were registered in this clinical survey is different from the limited patient background in clinical trials, thus it is considered that it is often a reference for daily practice.

## LS10-1

### The role of IL-6 in the pathogenesis of rheumatoid arthritis

Keishi Fujio

Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo

Conflict of interest: Yes

Since the molecular discovery of IL-6 in 1986, outstanding advances have been taken place in elucidating its functions in inflammation, im-

mune regulation, and organ homeostasis. Recently, evidence of a critical role of IL-6 in various inflammatory diseases including rheumatoid arthritis has been reported by the clinical application of the anti-IL-6 receptor antibody, tocilizumab. Furthermore, linkage between IL-6 receptor gene polymorphisms and rheumatoid arthritis has been elucidated in the context of increased IL-6 receptor expression and enhanced IL-6 signaling. In terms of environmental factor, the influence of commensals for IL-6 expression is emerging as a determinant of immune responses. This session will introduce a current overview of IL-6 biology especially in rheumatoid arthritis, focusing on how the data on IL-6 biology may facilitate our understanding of the potential benefits and risks of IL-6-targeting therapy.

## LS10-2

### Mode of action of biological agents revealed by advanced imaging technology

Masaru Ishii

Graduate School of Medicine & Frontier Biosciences, Osaka University

Conflict of interest: Yes

Recent development of diverse biological agents has been revolutionizing the clinical practices for treating RA. Nevertheless the actual modes of mechanism have been still elusive how each biologics act on specific target cell types and exert their respectively characteristic pharmacological effects. The presenter has so far originally established the system for visualizing inside of living bone tissues and joints by exploiting intravital two-photon microscopy, and elucidated cellular mechanisms on bone destructions by osteoclasts. Here I introduce the recent data showing the practical mode of actions of different biologics on inflammatory bone destruction in vivo, and, based on these fundamental data, discuss the future perspective on biological treatment of RA.

## LS11

### Post anti-inflammatory treatment pain in rheumatoid arthritis patients

Satoshi Ito

Department of Rheumatology, Niigata Rheumatic Center

Conflict of interest: Yes

Use of methotrexate became the standard of care for rheumatoid arthritis (RA) and then came the addition of biologic DMARDs (bDMARDs) for intractable patients. These treatments dramatically changed the clinical outcomes of RA. However, patients with a long history of RA with the joint destruction often suffer from pain, even though their synovitis is well controlled with anti-inflammatory therapies. Opioids have become popular in Western countries, and have also been approved for benign diseases in Japan. In 2011, tramadol hydrochloride/acetaminophen combination tablet (tramcet<sup>®</sup>) was approved and tramadol hydrochloride (tramal<sup>®</sup>) was approved in 2013. It is assumed that opioids ameliorate the pain in patients with a long history of RA without inflammation. Opioids might also be effective at the onset of RA, during disease flare-ups (until the effects of new anti-inflammatory therapy appear), or at the time when patients should discontinue bDMARDs. Pregabalin was approved in Japan for post herpetic neuralgia in 2010, and then later for neuropathic pain and fibromyalgia. We used pregabalin for pain due to compression fracture of the spine in RA patients and found that pregabalin was effective for joint pain to some extent. In order to confirm the existence of neuropathic pain in RA, we conducted a patient case survey made by Freynhagen et al. So far, we've collected 104 cases (male 21%, female 79%); 16% of the patients had radiating pain; 37% of the patients had tingling pain; 35 % had sudden painful attack like an electric shock and 30 % had dysesthesia. It is possible that neuropathic pain contributes, to some extent, the joint pain of RA patients. Teriparatides, some bisphosphonates or some anti-depressants (serotonin and norepinephrine reuptake inhibitors: SNRI) also showed an analgesic effect. These drugs might reduce the pain of RA patients who still suffer after receiving the current anti-inflammatory treatments such as bDMARDs.

## LS12

### Selection of csDMARDs and bDMARDs based on the T2T strategy in RA

Kazuyoshi Saito

The First Department of Internal Medicine, University of Occupational & Environmental Health, Fukuoka, Japan

Conflict of interest: Yes

Treatment to target (T2T) by measuring disease activity and adjusting therapy accordingly optimizes outcomes in rheumatoid arthritis (RA). The optimal strategy for preventing long-term joint damage and functional decline is unclear. Then BeSt study was conducted to compare clinical and radiographic outcomes of 4 different treatment strategies; sequential DMARDs monotherapy (group 1), step-up combination therapy (group 2), initial combination therapy with tapered high-dose PSL (group 3), and initial combination therapy with the TNF antagonist infliximab (IFX) (group 4) and brought about a lot of information regarding treatment strategies by cs and b-DMARDs. Initial combination therapy including either PSL (group 3) or IFX (group 4) resulted in earlier functional improvement than did group 1 and 2. The median increases in total sharp score were 2.0, 2.5, 1.0, and 0.5 in groups 1-4. Besides MTX, which is an anchor drug in RA, a lot of csDMARDs such as salazosulfapyridine, bucillamine, leflunomide, iguratimod, tacrolimus (TAC), tofacitinib (TOF) are now available in Japan. TOF, an orally administered JAK inhibitor, reduces disease activity rapidly as bDMARDs do. TAC, a calcineurin inhibitor, also inhibits functions of P-glycoprotein, which is involved in drug resistance and the cost got cheaper after approval of its generic compound. Regarding bDMARDs, three different kinds of mode of action of 8 biologics are available in Japan. In terms of efficacy of these agents, it has been shown there is no difference among them in the recent report. However, it is a very important issue how to select biologics in daily clinical practice. The factors should be considered regarding choice of biologics are mode of action, pharmaceutical properties such as structure, half life time, immunogenicity etc, tolerance to MTX, safety, methods of administration, medical economics. In the lecture, I will discuss where each DMARDs fits into RA treatment based on its pharmaceutical proper.

## LS13

### Updated therapeutic strategies for pulmonary hypertension in patients with connective tissue disease

Masataka Kuwana<sup>1</sup>, Yasushi Kawaguchi<sup>2</sup>, Sumiaki Tanaka<sup>3</sup>, Hiroaki Dobashi<sup>4</sup>

<sup>1</sup>Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, <sup>2</sup>Institute of Rheumatology, Tokyo Women's Medical University, <sup>3</sup>Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, <sup>4</sup>Department of Internal Medicine, Faculty of Medicine, Kagawa University

Conflict of interest: Yes

Prognosis of pulmonary hypertension (PH) associated with connective tissue disease (CTD) is very poor if remain untreated, with a survival of <20% at 3 years after diagnosis. Recent introduction of molecular-targeting pulmonary vasodilators has improved functional capacity and hemodynamics in patients with pulmonary arterial hypertension (PAH) associated with CTD. In addition, increased recognition of PH/PAH by rheumatologists has resulted in promotion of active screening program, which enables us to diagnose and treat PAH early. However, long-term survival of PAH associated with CTD is still unsatisfactory even in recent cohorts. To further improve prognosis, it is imperative to practice personalized medical approach by appreciating complex nature of PH in patients with CTD. In patients with PAH associated with non-systemic sclerosis (non-SSc) CTD, including systemic lupus erythematosus, mixed connective tissue disease, Sjogren's syndrome, pulmonary vascular remodeling is often reversible, especially in early disease phase. In this case, up-front combination therapy with two or more pulmonary vasodilators should be initiated in combination with immunosuppressive treatment to achieve remission, which is normalization of exercise capacity and hemodynamics. In contrast, SSc patients with PH often have complex pathophysiology consisting of PAH, pulmonary veno-occlusive disease, myocardial involvement (usually diastolic dysfunction), and interstitial lung disease,

leading to an inadequate or sometimes adverse response to pulmonary vasodilators. Since it is difficult to accumulate clinical evidence from placebo-controlled, randomized clinical trials involving a large number of CTD patients with PH/PAH, it is highly valuable to share clinical experiences based on individual cases among rheumatologists. This seminar features case presentations of PH/PAH associated with non-SSc and SSc, which should be useful in our daily practice.

## LS14

### Novel findings of abatacept in RA patients

Désirée Van der Heijde

Leiden University Medical Center

Conflict of interest: Yes

With the availability of several biological DMARDs it is important to know the comparative efficacy. AMPLE is a blinded 2-year head-to-head noninferiority study comparing SC abatacept with adalimumab on background of methotrexate. Both the 1-year and 2-year results show that there were comparable responses seen across all efficacy measures, including ACR and DAS28 (CRP) responses and inhibition of radiographic progression. Fewer patients on abatacept discontinued due to adverse events (3.5%) than on adalimumab (9.1%). Another important aspect is to know if induction of clinical remission followed by withdrawal of treatment can lead to drug-free remission in early RA. This was tested in the AVERT trial: patients were treated with abatacept plus MTX, abatacept monotherapy or MTX for 12 months and all medications (including biologic, MTX and steroids) was withdrawn in patients in DAS28-CRP remission (<2.6). In the aba+MTX group 61.3% reached remission at 12 months in comparison to 42.1% in the aba-mono and 45.7% in the MTX group. After withdrawal of all treatment, 25% of the patients in remission at month 12 were still in remission at month 18. This was 28% in the aba-mono and 17% in the MTX groups. AVERT is the first study to show sustained remission following withdrawal of all therapy.

## LS15-1

### Establishment of the referral system for femoral fractures in Shibata area in Niigata prefecture

Satoshi Ito

Department of Rheumatology, Niigata Rheumatic Center

Conflict of interest: Yes

In shibata area, patients with hip fracture are treated in the Niigata Prefectural Shibata Hospital. After the emergent operation, patients are transferred to the rehabilitation ward of the Niigata Rheumatic Center for rehabilitation. However, there was no treatment for osteoporosis and follow up. We started the referral system of the patients to general practitioners (GP) and asked them to start bisphosphonates. We held seminars of osteoporosis and hip fracture for 5 times in northern part of Niigata prefecture (wider than shibata area). GP who prescribe drugs have economical disadvantages when their prescription exceeds more than 7 drugs (So called 7 drugs rule). Therefore, we recommended the use of combination drugs for hypertension, diabetes mellitus or hyperlipidemia. Sixty patients (male: 10, female: 50) with hip fracture were analyzed between February 2013 to March 2014. Twelve % of the patients did not have any traumatic episodes for fracture and 7 % had second hip fracture. Ninety three % of the patients had complications such as hypertension or diabetes mellitus and 92 % of the patients had their GP. The referral were done only 41.6 % of the patients due to their age, dementia, or family's decision. According to the development of BP, now we can use BP taken every 4 weeks (minodronate) or monthly BP (risedronate). Improvement of adherence is expected. In addition to that, the intravenous BP (alendronate and ibandronate) became available. We can expect the intravenous BP as a new treatment choice for the patients in conflict with above mentioned 7 drugs rule, for the patients with gastrointestinal side effects of oral BP, or for the dementia patients who have a concern about the decrease of adherence. This referral system might reduce the second hip fracture in Japan just like other Western countries.

## LS15-2

### Strategic bisphosphonates therapy for secondary osteoporosis

Ikuko Tanaka

Nagoya Rheumatology Clinic, Initiative for Rheumatology and Osteoporosis, Aichi, Japan

Conflict of interest: None

Glucocorticoid-induced osteoporosis (GIO) is the most common secondary osteoporosis, as glucocorticoid is a medication prescribed in every hospital department. It can be referred to as an iatrogenic disease. Proposals or guidelines for GIO have been presented in several countries. In 2014 revised guidelines on the management and treatment of glucocorticoid-induced osteoporosis was published by the Japanese Society for Bone and Mineral Research. Oral drugs of alendronate and risedronate are first-line, which have evidences that they are effective for the primary and secondary prevention of bone fractures. On the other hand, negative points of bisphosphonates are adverse effects such as digestive symptoms and low absorption rate. The patients with GIO have underlying diseases, for which glucocorticoid and other medications are necessary. The underlying diseases and the medications may affect intestinal absorption, which results in lowering further bio-availability of bisphosphonates. Clinical trials of secondary prevention of bone fracture due to GIO demonstrated that ibandronate significantly increased bone mineral density of the lumbar spine and the femur. Ibandronate was placed as a substitution drug because the underlying diseases of the patients were limited and the number of the patients was small. However ibandronate, administration of which is monthly venous injection and high bio-available, can be very beneficial to patients with GIO. In this lecture, I would like to talk about the therapeutic strategy of bisphosphonates for secondary osteoporosis. Cases suitable for ibandronate will be discussed.

## LS16

### Screening and prophylaxis for pulmonary infectious diseases in patients with rheumatic diseases given immunosuppressive treatment

Masayoshi Harigai<sup>1,2</sup>

<sup>1</sup>Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, <sup>2</sup>Department of Rheumatology, Tokyo Medical and Dental University Hospital

Conflict of interest: Yes

Patients with systemic rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) can develop various types of pulmonary infections (PI) during immunosuppressive treatment. Pulmonary infections not only hamper treatment of underlying rheumatic diseases, but also affect vital prognosis of patients. We implemented the PREVENT study with 11 medical institutions in Japan, and enrolled 763 in-patients who started immunosuppressive treatment for active systemic rheumatic diseases and followed for 1 year to identify risk factors for PI. During the observation period, 61 patients developed PI. Cox hazard regression analysis using baseline data showed that age  $\geq 65$  years-old,  $\geq 20$  pack-years of smoking, serum creatinine, and maximum prednisolone dose during the first 2 weeks of treatment were significantly associated with PI. Special attention should be paid to opportunistic infections during immunosuppressive treatment of systemic rheumatic diseases. Japan has moderately high incidence of tuberculosis in the world and optimal screening and monitoring for tuberculosis (TB) are required prior to commencing immunosuppressive treatment to decrease risk for TB in the patient population. For screening of TB, medical interview, chest X-ray or tomography, and interferon- $\gamma$  releasing assay (IGRA) or tuberculin skin test (TST) are recommended. In a meta-analysis that compared predictive values of IGRA and TST for development of active TB, IGRA showed superior predictive values, especially in patients with high risk. Incorporating both IGRA and TST for screening and treating latent TB in patients positive for either tests was reported to provide a favorable outcome in patients given TNF inhibitors. Frequent conversion of IGRA and TST has been reported and repeated measurement should be considered if necessary. In this seminar, I would like to discuss recent evidence about PI and IGRA in systemic rheumatic diseases.

## LS17

### Characteristics and treatment of elderly patients with rheumatoid arthritis

Naoto Tamura

Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine, Tokyo, Japan

Conflict of interest: Yes

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease accompanied with progressive bone and cartilage destruction characterized by erosive synovitis. Recently, it has been shown that beginning of anti-rheumatic drugs, mainly methotrexate and biologic DMARDs, in early disease can prevent subsequent disease progression. Although the peak onset of RA is between the ages of 30 and 50 in females, elderly RA patients with long disease duration are increasing due to the aging population. Furthermore, elderly-onset RA is also increasing and the prognosis has been shown to be poor. Obviously, elderly patients have more complications, impaired drug metabolism, and declined immunological function, which is called immunesenescence, causing increased risk of infection and malignancy. Since adverse effects, especially life-threatening severe infections are more common in elderly patients, less aggressive therapy is likely to be selected even if the disease activity is beyond moderate. The continuation of the disease activity may result in impaired physical functions, unstable mental conditions, poor nutrition, and deterioration of social activity, leading to increased mortality. However, recently elderly patients are becoming to be successfully treated with appropriate anti-rheumatic drugs as preventing of infections and carefully monitoring the side effects. In patients with mild disease or in case sufficient methotrexate or biologic DMARDs is intolerant, bucillamine, salazosulfapyridine, tacrolimus, mizoribine, and gold sodium thiomalate are commonly used either in monotherapy or combination therapy. Treatment of elderly RA should be determined individually based on the disease severity and the existence of renal dysfunction, lung disease and other complications. Moreover, patient education is essential to prevent the side effects. In this seminar, I would like to talk characteristics of elderly RA and its management in daily practice.

## LS18

### Role of tacrolimus in treatment of intractable connective tissue diseases - SLE and PM/DM -

Tsuneyo Mimori

Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Conflict of interest: Yes

Tacrolimus is an immunosuppressive drug classifying into the calcineurin inhibitors. This drug forms a complex with FK-binding protein in cytoplasm, inhibits calcineurin involving dephosphorylation and nuclear translocation of NF-AT, and suppress T cell function. In Japan, tacrolimus is approved to use for the inhibition of rejection in transplantation, rheumatoid arthritis, lupus nephritis (LN), myasthenia gravis, ulcerative colitis and polymyositis/dermatomyositis (PM/DM)-associated interstitial lung disease (ILD). In SLE, the treatment strategy of LN to prevent renal insufficiency is very important. The efficacy of tacrolimus in LN has been demonstrated in the results of both clinical trials and post-marketing surveillance. However, the effects on decreasing proteinuria and steroid-sparing effect are indicated, remission of severe LN does not reach intravenous cyclophosphamide (IVCY) and long-term prognosis of tacrolimus users is still unclear. Recently, the multi-target therapy combining high-dose glucocorticoids (GC), mycophenolate mofetil and tacrolimus has been reported to be more effective in severe LN than GC and IVCY. ILD is the most important organ disease in PM/DM affecting life prognosis. The efficacy of tacrolimus is proven both in GC-resistant myositis and ILD. Clinical aspects of ILD in PM/DM are dependent on the specific autoantibodies. ILD in PM/DM with anti-ARS antibodies shows relatively good response to high-dose GC, but shows frequent recurrence. Early users of immunosuppressants including tacrolimus revealed better prognosis than late or never users, suggesting that the use of both GC and early immunosuppressants including tacrolimus is recommended in anti-ARS-positive PM/DM-ILD. Anti-MDA5 antibody is specifically detected in patients with clinically amyopathic DM and associated with rapidly



progressive ILD. In these patients, early use of the combination of high-dose GC, IVCY and tacrolimus may improve the life prognosis.

## LS19

### Treatment strategy for osteoporosis - guidelines and Lifetime Bone Care -

Satoshi Soen

Department of Orthopaedic Surgery and Rheumatology, Nara Hospital, Kinki University School of Medicine

Conflict of interest: Yes

Osteoporosis includes primary and secondary osteoporosis, and causes of secondary osteoporosis include rheumatoid arthritis and glucocorticoid, etc. In Japan, guidelines for prevention and treatment of osteoporosis were revised in 2011, and a new revised edition is going to be published in 2015. About secondary osteoporosis, 2014 revised guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research was published. The treatment objective of osteoporosis is prevention of osteoporotic fractures, and the important fractures that should be prevented include hip fracture in the older patients and vertebral fracture in the younger patients. About primary osteoporosis, the evidence of the hip fracture preventive effect is found in alendronate, risedronate, denosumab and the evidence of the vertebral fracture preventive effect is found in bisphosphonates, SERM, eldelcalcitol, teriparatide, denosumab. Also, about male osteoporosis, alendronate, risedronate, recombinant teriparatide have preventive effect of vertebral fracture. In addition of these drugs, ibandronate, alfacalcidol, calcitriol have preventive effect of vertebral fracture in glucocorticoid-induced osteoporosis. It is necessary to consider the dosage forms of the drugs on the occasion of drug choice. I will present a real cases and comments on drug choice for fracture prevention for the lifetime bone care.

## LS20-1

### Challenge for higher stage of functional remission by upper extremity surgery for rheumatoid arthritis

Keiichiro Nishida

Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

Conflict of interest: None

Comprehensive disease control (CDC) for rheumatoid arthritis (RA) is defined as DAS28-CRP  $<2.6$  for clinical remission, Health Assessment Questionnaire disability Index (HAQ-DI)  $<0.5$  for functional remission, and change from baseline in modified Total Sharp Score  $\leq 0.5$  for structural remission. Normal physical function assessed using the HAQ-DI seemed to be the most difficult component to achieve, particularly in established long-standing disease. We reviewed the 106 RA patients who have undergone the upper extremity surgery in our institute during 2011 to 2013. They were 95 women and 11 men, and the mean age and disease duration were 59.5 years and 19.2 years, respectively. Sixty-four percent of the patients used MTX, and 24% were under control by biologic DMARDs. Pain VAS, DASH and Hand 20 were used as patient-reported outcomes those might be sensitive to the effects of treatment than physician-assessed measures, and assessed pre-operatively and one-year post-operatively. The mean DAS28-CRP improved from 3.0 preoperatively to 2.4 postoperatively ( $P<0.01$ ), but HAQ-DI did not change. Forty-seven patients (44.3%) underwent surgery even under HAQ-DI remission. HAQ-DI was further improved postoperatively in 17 patients (29.8%), and 14 patients achieved HAQ-DI  $<0.21$ . Then patients were divided into three groups according to the joint involved; Elbow group ( $n=27$ ), Wrist group ( $n=24$ ), and Finger group ( $n=55$ ). Pain VAS and DAS28-CRP were significantly improved by the wrist and elbow surgery. DASH and Hand 20 were significantly improved in the all three groups. Active motion, pain, and cosmetic items were particularly improved in Elbow, Wrist, and Finger group, respectively. Our data might be useful for prospection of the effect of the surgery, and might contribute the patient's satisfaction for the surgery, as well as achievement of higher stage of functional remission.

## LS20-2

### Outcome of rheumatoid arthritis surgery, Improvement of QOL by esthetic and functional restoration

Hajime Ishikawa

Department of Rheumatology, Niigata Rheumatic Center, Shibata, Japan

Conflict of interest: None

With the use of biologic agent (Bio) for the treatment of rheumatoid arthritis, uncontrollable synovitis in the past came to be well controlled. However, some patients were still difficult to reach the treatment target and received surgical treatment and rehabilitation for deteriorated joint and deformity, even if the patients were medicinally treated based on the concept of treat to target (T2T). Recently, patients desired functional remission aiming at higher level of quality of life (QOL). As a result, while the number of surgery at the large joints or the sole synovectomy decreased, the number of small joint surgery including correction of joint deformity and reconstruction in the hand and the foot increased in our rheumatic center. For the surgically treated joint, ultrasonography was done before the operation at 301 joints. Synovium was obtained at the operation and examined histopathologically. In the joints with the use of Bio ( $n=68$ ), grade of power doppler (PD) signal and Rooney score excepting proliferating blood vessels were lower than those without Bio. In the sunovium with the use of tocilizumab ( $n=18$ ), infiltration of lymphocytes was low and fibrosis was high Patient reported outcome survey was performed on 40 patients with upper extremity surgery prospectively. Surgical site was shoulder in one patient, elbow in 9, wrist in 11 and hand in 8. DASH (disability in the upper extremity), J-HAQ (physical function/QOL), EQ-5D (QOL), DAS28-ESR (4) and SDAI (disease activity) significantly improved at one year after surgery ( $p<0.01$ ), despite there was no change in BDI-II (mental/depression), Surgical reconstruction should be considered to get rid of impairment of physical function due to irreversible structural damage of the joint, while disorder due to inflammation could be solved by Bio. Combination of medication and surgical treatment is a great gospel for the patients aiming at functional remission of RA.

## LS21

### Topics on diagnosis and treatment in patients with Sjögren's syndrome in 2015

Takayuki Sumida

Department of Internal Medicine, University of Tsukuba

Conflict of interest: Yes

Sjögren's syndrome (SS) is an autoimmune disease that affects exocrine glands including labial salivary glands (LSGs) and lacrimal glands (LGs), resulting in dry mouth and dry eyes. In patients with SS, there are a lot of autoantibodies such as anti-nuclear antibodies, rheumatoid factors, anti-SS-A antibodies, anti-SS-B antibodies, and anti-M3 muscarinic acetylcholine receptor (M3R), and autoreactive T cells in LSGs and LGs. The surveys on epidemiology of SS demonstrated that the mean age of SS patients is 60 years old, the ratio of male:female is 1:17.4, and the number of SS is about 70,000 persons. In Japan, the criteria for the diagnosis of SS was determined by the revised Japanese Ministry of Health criteria for the diagnosis of SS in 1999. In this criteria, there are four factors as followings: 1) Histological findings in LSGs or LGs. 2) Oral examination such as sialography or scintigraphy and Gam test or Saxon test. 3) Ophthalmological examination such as Shirmer test and staining test. 4) anti-SS-A antibodies or anti-SS-B antibodies. The positivity of more than two items is necessary for diagnosis of SS. The validation of Japanese criteria, American-European Consensus Group classification criteria for SS (AECG) and ACR criteria in Japanese patients showed that the sensitivity and specificity of Japanese criteria was the highest. In treatment of patients with SS, there are two approaches. One is to improve QOL and eye drops for dry eyes and pilocarpine hydrochloride and cevimeline hydrochloride for dry mouth. The other is to therapy against systemic organ involvement. In this case, adrenocortical steroid and/or immunosuppressive drugs should be necessary to control inflammation. Near future, biologics against B cells (rituximab, belimumab) and T cells (abatacept) will be approved for SS therapy. In this luncheon seminar, I would like to review the topics on diagnosis and therapy in patients with SS.

## LS22

### **Tramadol hydrochloride/acetaminophen combination tablets on Rheumatoid Arthritis (RA) patients with low back pain, neuralgia and joint pain.**

Atsushi Kaneko

Dept. of Orthop. Surg. And Rheumatology, Nagoya Medical Center, National Hospital Organization

Conflict of interest: None

NSAIDs is strongly recommended for its efficacy of clinical symptoms of RA patients by the new Japanese guideline 2014 for Rheumatoid arthritis (RA) clinical practice. So, use of analgesics are still highly required to control pain before disease activity is subsided or pain associated with joint destruction. In NinJa (National Database of Rheumatic Diseases by iR-net in Japan), the frequency of NSAIDs treatment has been decreased with improvement of disease activity of RA for the past decade from 72.6% in first year to 37.5% in last year. However, several elderly patients with renal failure still medicate NSAIDs. I can't recommend to use NSAIDs for a long term due to its risk of gastrointestinal or renal disorders and cardiovascular events. Recently, NSAIDs seems no more necessary for most patients with RA remaining low disease activity or remission in our practice. However, they often complain low back pain by degenerative disease of lumbar spine due to aging or neuralgia. Many patients suffering from joint destruction pain with long disease duration request prescribing analgesics. As for acute pain, I recommend to use NSAIDs, effective for my LBP, external medicine using for a short period with small dosage. But, if pain still persist, I try switching or adding Tramcet® rather than continuing NSAIDs. In this session, I would like to introduce 28 RA patients mainly diagnosed as LBP, neuralgia and joint pain, prescribed tramcet®. 3 of 28 patients were withdrawn due to adverse events (2 nausea, 1 dizziness) in early treatment, and 1 excluded due to combination therapy of Lyrica®, efficacies in 24 patients (mean age 73.9 ± 8.5 years, 11 back pain+ leg pain, 8 joint pain, 4 mixing, 1 other) were evaluated. In pain VAS at 12 weeks, more or less than 20% improvement, no change and worsen were 11, 5, 6 and 2 patients respectively. In this lecture, I would like to state lumbar spine pathology in RA patients including how to use Tramcet®.

## LS23-1

### **Visualization of Early Signs of Joint Inflammation with Novel Doppler Ultrasound Technology Superb Micro-vascular Imaging (SMI) in Rheumatoid Arthritis**

Akihiro Narita

Hokkaido Medical Center for Rheumatic Diseases

Conflict of interest: None

In recent years, joint ultrasonography have been increasingly employed in the medical management of patients with rheumatoid arthritis (RA). Ultrasonography provides detailed visualization of soft tissues over a wide range and further synovial inflammation in the early stages of disease that cannot be detected by physical examination. Diagnostic joint ultrasonography therefore play a key role in establishing the diagnosis of RA and evaluating therapeutic effects. Toshiba's advanced technology of Superb Micro-vascular Imaging (SMI) is a novel Doppler technology for visualizing blood flow. Compared with the traditional power Doppler technology, SMI can depict smaller vessels with lower blood flow velocity. SMI has the advantages of a superior ability to visualize low-velocity flow, a higher frame rate of 50 image frames per second, and a high resolution with low motion artifacts. In the practical examination of joint ultrasonography in RA, SMI directly detect abnormal synovial vascularization with low motion artifact. The PLT-1204BT transducer, which is designed for use with the latest model in the Aplio Platinum series of diagnostic ultrasound systems, provides higher resolution images than before. B-mode imaging with this transducer can clearly depict the proliferation of synovial tissues and tendon sheaths and also detect small bone erosions that are not visible in X-ray images. In addition to these imaging advancements, ultrasonography provide real-time joint information to both physicians and patients that help physicians to explain for the disease and help patients to understand the disease. Such relation leads to better clinical practice in RA. In this session, we will focus on the clinical usefulness of diagnostic ultrasonography of color Doppler joint imag-

ing of the patients with RA and discuss the value of Toshiba's advanced technology of SMI

## LS23-2

### **Utility of new Dopplar imaging SMI and future of ultrasound imaging**

Michihiro Ogasawara

Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine, Tokyo, Japan

Conflict of interest: None

How to make a diagnosis and decide on courses of treatment for joint problems? When we assess the diagnosis and disease activity, it is important to search for high yieldable clinical information. Which part of joint, and what kind of alteration is existing and related to symptoms? In order to understand it, it is hard only from the information of history taking, clinical examination and hematological examination. Ultrasound (US) will enable us to obtain the objective, reliable high quality anatomical image immediately and give us the high yieldable information. Abnormal hypoechoic or anechoic (relative to subdermal fat) intraarticular material, that is displaceable or not, compressible or not, exhibit Doppler signal or not, are important for judgment of pathological findings. This US technic needs a certain amount of time or energy. Much is the same is true to examine multiple joints exhaustively and possible not to obtain yieldable information. In order to disperse utility of US, feasibility and efficiency are problems to solve. Not only to increase the contribution rate by examining multiple joints, but to obtain high contribution rate only by a few joints' examination, advancement of US equipment is of considerable importance. Toshiba's advanced technology of Superb Micro-vascular Imaging (SMI) is a novel Doppler technology for visualizing blood flow. Compared with the traditional power Doppler technology, SMI can depict smaller vessels with lower blood flow velocity. In addition, blurring of vascular structures image due to the Doppler phenomenon is minimized, permitting detailed visualization of the courses of blood vessels. In years to come, it's an ideal that a picture close to histopathological findings will be obtained by US. SMI is the modern technology can expect to open new imaging territory. In this lecture, experienced cases are shown and consider about utilizing methods of SMI by comparing SMI with conventional power Doppler technology.

## LS24

### **Update of diagnosis and treatment for connective tissue disease-associated pulmonary hypertension**

Yasushi Kawaguchi

Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: Yes

The diagnosis and treatment of pulmonary hypertension (PH) associated with connective tissue disease (CTD) have been remarkably improved in this decade. Systemic sclerosis (SSc), mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE) are representative of PAH associated with CTD. However, in patients with SLE alone immunosuppressive therapy is very effective, we speculate the pathologic of SLE-PAH have guessed the merger of vasculitis. As collagen disease presenting with myocardial injury, there are SSc, polymyositis (PM), and dermatomyositis (DM). Although myocardial impairment becomes in these diseases, they exhibited a condition of cardiomyopathy rarely complicating severe PH. Reduction in pulmonary vascular bed caused by pulmonary fibrosis could result in PH. Collagen diseases exhibiting pulmonary fibrosis can be SSc, PM, DM, rheumatoid arthritis (RA), and the ANCA-associated vasculitis. This condition, the cause PH is, SSc is almost a is, PM, DM, RA, in ANCA-associated vasculitis is a rare. If the PH is caused by thrombosis of the pulmonary artery, the CTD is assumed the case of the anti-phospholipid antibody syndrome. However, it is rare. The true PH due to systemic vasculitis, which is classified as others, can be complicated with systemic lupus erythematosus (SLE), Takayasu's arteritis and ANCA-associated vasculitis. In the treatment of PAH, we have selected upfront therapy by the pulmonary artery vasodilator. In the case of PH due to cardiomyopathy, pulmonary fibrosis, and thrombosis, we should perform their therapeutic agents. As a result, we considered if it can not be suppressed, the progress of the PH should be considered a

combination of pulmonary vasodilator. On the other hand, if it is considered to be related to vasculitis, it is performed mainly immunosuppressive therapy in accordance with the treatment of vasculitis.

## LS25

### Clinical performance of certolizumab pegol

Hideto Kameda

Toho University Ohashi Medical Center, Tokyo, Japan

Conflict of interest: Yes

Certolizumab pegol (CZP) is a biological agent composed of a single Fab' of a humanized anti-tumor necrosis factor (TNF) monoclonal antibody (MW ~50k) and 2 molecules of polyethylene glycol (PEG; MW ~40k). The presence of PEG leads to the improvement of solubility, the decrease in the distribution of CZP into non-inflamed peripheral tissue and in the immunogenicity and degradation/uptake of CZP by the protection of various epitopes, all of which are characteristics of CZP. A rapid onset of effect as other anti-TNF biologics is one of the clinical features of CZP as a therapeutic agent for rheumatoid arthritis (RA). Indeed, most of the patients achieving low disease activity at 1 year on CZP therapy show the improvement of DAS28 (disease activity score of 28 joints) by 1.2 or greater at 12 weeks, and furthermore, at least by 0.6 at 6 weeks. CZP is the only subcutaneously administered biological agent approved for RA with a loading strategy, and it is reasonable to determine the initial effect of CZP at 6 weeks, just after the completion of 3 loading injections. Therefore, concomitant synthetic anti-rheumatic drugs should be intensified, at least, for patients showing primary lack of efficacy at 6 weeks. Although the onset of CZP effect is rapid with or without concomitant methotrexate (MTX), it should be noted that the further improvement in disease activity after 6 weeks of CZP treatment is modest without MTX, as with the cases of other anti-TNF biologics. Postmarketing surveillance of CZP for RA patients in Japan is ongoing since March 2013. An interim report on CZP effectiveness in TNF-IR (inadequate response) and other patients and safety profiles of CZP focusing on infectious diseases will be provided in comparison with the evidences of CZP in other countries and those of other anti-TNF agents in Japan.

## LS26-1

### Treatment of SLE: Current Situation and Future Prospects

Tsutomu Takeuchi

Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine

Conflict of interest: Yes

SLE is a systemic autoimmune disease, characterized by a variety of clinical manifestations with organ involvement. Five-year life expectancy was below 50% in 1950-60, but it has improved to above 95% by the introduction of steroid-pulse therapy, novel immune-suppressants and various supportive therapies since then. Nevertheless, it is recognized that the patients do not fully accept the quality of life and long-term survival. In addition, standardization of treatment remains to be established because the severity of inflammation and organ damage may greatly vary among individual patients. The issues surrounding clinical practice in SLE impose the huge burden with careful selection of appropriate induction treatment for the individual patients. Also it is true for maintenance therapy using continuous glucocorticoids, which may lead to osteoporosis, diabetes, and/or infections. These co-morbidities may deteriorate the functional prognosis of the patients. Considering these points, more specific and tolerable treatment strategy for SLE is required. Huge efforts have been taken to elucidate the molecules involved in the pathogenesis of SLE and identified promising targets such as BAFF and IFN $\alpha$ . In 2011, anti-BAFF antibody approved in EU/US as the first novel drug during this half century, whereas anti-CD20 antibody, which had shown efficacy in investigational clinical researches, finally ended up with a disappointing failure in a phase 3 study. Now difficulty of the development of novel SLE drugs is also revealed, especially in selection of outcome measures, background of enrolled patients, etc. With this situation in mind, this lecture reviews current treatment options and limitations and also covers future prospects for early diagnosis, remission and new therapies of SLE.

## LS26-2

### Dual-targeted approach to SLE: finding synergy in molecular and clinical treatment targets with special focus on Treat-to-Target

Thomas Dörner

Dept. Medicine, Rheumatology and Clinical Immunology, Charite Berlin and DRFZ, Berlin, Germany

Conflict of interest: Yes

The pathogenesis of SLE is highly complex and arises from an abnormal immune response in a person with predisposing genetic factors. Loss of immune tolerance, increased autoantibody and immune complex production, and defective memory T, B and plasma cell processes together with activated innate immunity result in inflammation, tissue injury and organ damage. New biologic treatments have been or are in development to target these immune abnormalities to control the disease. Therapies that act on B cells through depletion or modulation represent the bulk of candidate agents. Traditionally, SLE treatment regimens have relied heavily on corticosteroids (CS), despite the fact that they are well known to cause permanent organ damage and increase the risk of infections, cardiovascular, bone, metabolic etc. complications. While there is lack of guidance on CS dosing in SLE, latest data show that CS doses  $\geq 6$  mg/day increase the risk of organ damage. Since several studies of the biologic agents have reported clinically meaningful reductions in CS doses, the "dual target" potential of biologic therapy in reducing both SLE disease activity and CS dose is very attractive. This dual approach perfectly fits in recently established principles of treat-to-target (T2T) in SLE after such strategy has been applied to many diseases to serve improved patient's care and outcomes. This T2T consensus agreed on basic principles to treat SLE and should be taken into consideration in clinical trials and in clinical practice. Based on a comprehensive systematic literature review four overarching principles and 11 recommendations for T2T in SLE were developed. The main areas of these recommendations are targeting remission, prevention of damage and improving quality of life. While innovative therapeutic approaches are still needed for SLE, the T2T initiative addresses important aspects of current treatment modalities and their optimal use in order to achieve better outcome for our SLE patients.

## LS27

### HBV reactivation during chemotherapy and immunosuppressive treatment

Yukio Osaki

Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital

Conflict of interest: Yes

Hepatitis B virus is well known as one of the main causes of acute hepatitis, chronic liver disease and liver cancer which are diagnosed by the presence of HBsAg in the blood. HBsAg positive patients, or HBV carriers, generally infected by mother to child transmission in Japan are recommended to receive regular follow ups, regardless of the presence of normal liver function. On the other side, infected adults become HBsAg positive and elevation of liver enzymes (acute hepatitis), following HBsAg disappears and liver function test normalize and it's recognized as "cure" (transient infection). Seroconversion of HBsAg to HBsAb together with HBeAb positive has been considered as a past history of HBV infection. However, in recent years, under the advent of powerful chemotherapy and immunosuppressive therapy, patients believed to have been cured are seeing HBV reactivation, so called de novo hepatitis. Moreover, the mortality rate of de novo hepatitis is very high, so it has gained the attention of the mass media and caused social concern. Even if the HBsAg disappears, the presence of the HBe antibody does not mean a past history of infection but has been suggested that HBV was a latent infection. This has already been made apparent from the experience of living donor related liver transplantation at Kyoto University. Recipients of liver transplants from HBsAg-negative, HBeAb-negative donors do not develop Hepatitis B, but most recipients from HBsAg-negative, HBeAb-positive donors do develop Hepatitis B. Furthermore, HBVDNA is detected in healthy HBeAb-positive liver tissue, and the existence of HBeAb shows that HBV remains in the liver. This means that the conventional wisdom of HBsAg loss = cure of HBV infection is over-

turned, and the disappearance of HBsAg does not mean the extermination of HBV infection. In HBcAb positive cases, it has become clear that the virus exists in the liver in the state of a latent infection.

### LS28-1

#### csDMARDs use in Tokyo Metropolitan Tama Medical Center

Shoji Sugii

Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan

Conflict of interest: None

We realize that RA treatment changes in the medication after an appearance of the biological DMARDs. Accumulation of knowledge about the biological DMARDs and the expansion of the kind seem to change the direction for uses. It seems to be to change positioning of csDMARDs at the same time. Our Hospital registered 944 cases with National Database of Rheumatic Diseases by iR-net in Japan (NinJa) in 2013, as for the antirheumatic drug utilization, as for 95%, the steroid utilization, as for 48%, the biological preparation utilization, as for 23%, MTX utilization, 69%, the utilization of csDMARDs except MTX were 50%. There is not little at all use of csDMARDs in this way. I will consider positioning of current csDMARDs in our Hospital.

### LS28-2

#### The impact of the combination therapy of conventional synthetic disease-modifying antirheumatic drug with anchor drug, MTX in Japan

Atsushi Kaneko

Dept. of Orthop. Surg. And Rheumatology, Nagoya Medical Center, National Hospital Organization

Conflict of interest: None

According to Guidelines for the management of rheumatoid arthritis, Japan College of Rheumatology 2014, combination therapy with methotrexate (MTX) and the other conventional synthetic disease-modifying antirheumatic drug (csDMARD) in patients with MTX resistant rheumatoid arthritis (RA) is described to have important implications in the strategies for RA. However, adverse events increase while the effects increase, and no significant difference has been shown in loss of effects or discontinuation due to toxicity between MTX monotherapy and combination therapy, for which the strength of recommendation was determined to be weak. On the other hand, the frequent use of bDMARD has problems of expensive costs and deterioration and relapse due to discontinuation also in Japan, and it is obvious that bDMARD therapy cannot be indicated for all patients. In 13286 RA patients registered in Japanese large cohort of NinJa (National Database of Rheumatic Diseases by iR-net in Japan), 32.0% of the patients had been medicated MTX monotherapy, 16.4% had the combination therapy with MTX + bDMARD, 15.9% had combination therapy with MTX + csDMARD, and 19.1% monotherapy or combination therapy with csDMARD other than MTX. Extraction of combinations with Boolean remission rate higher than 20% from these therapies showed that MTX + SSZ, MTX + BUC, MTX + SSZ + BUC, and MTX + BUC + TAC had high efficacy. In addition, from the point of view of safety, the hospitalization rate of each combination was generally around 5%, which was not much different from the rate in the overall NinJa. On the whole, in NinJa2013, combination therapy with DMARD in which 2 or 3 drugs are selected from 4 drugs of SSZ, BUC, TAC, and mainly MTX, the anchor drug, has been actively performed also in Japan, and csDMARD, MTX, and SSZ evaluated as strongly recommended in Guidelines for the management of rheumatoid arthritis, Japan College of Rheumatology 2014 have already played the central roll.

### LS29

#### Current management of Vasculitis

Jan Willem Cohen Tervaert

Maastricht University, Maastricht, the Netherlands

Conflict of interest: None

The ANCA-associated vasculitides, granulomatosis with polyangiitis

(GPA, formerly Wegener's), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss), are a group of multi-system autoimmune diseases characterized by necrotizing small- to medium-vessel vasculitis and the presence of anti-neutrophil cytoplasmic antibodies. Genetic and environmental factors are involved in their etiopathogenesis, with a possible role for silica exposure in AAVs and *Staphylococcus aureus* infection in GPA. The distinct associations of PR3-ANCA and MPO-ANCA with different HLA class II antigens, which are stronger than those with the associated diseases, suggest a pathogenic role for those ANCAs. Both ANCA and T cells seem to be involved in lesion development. Current therapeutic strategies consist of glucocorticoids in conjunction with either conventional or biologic agents. Once considered life-threatening diseases, the introduction of stage-adapted immunosuppressive therapy and medications with decreased toxicity has improved patients' survival. Treatment is biphasic, consisting of induction of remission (3-6 months) for rapid control of disease activity and maintenance of remission (at least 18 months) to prevent disease relapse using therapeutic alternatives that have reduced toxicity. I will review current treatment strategies for these diseases, with a special focus on long-term follow-up data from randomized controlled trials and new developments in remission induction and maintenance therapy. Since current treatment strategies still have substantial short-term and long-term adverse effects, and relapses are still frequent, less-toxic and more-effective approaches are needed. Future research directions include investigation of the optimal duration and frequency of maintenance therapy as well as development of targeted therapeutic agents, which is enhanced by emerging insights into disease pathogenesis.

### LS30-1

#### Pharmacoeconomical analysis in the management of rheumatoid arthritis

Hisashi Yamanaka, Eiichi Tanaka

Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: Yes

Control of the disease activity of rheumatoid arthritis (RA) has been improved largely by the introduction of newer class of drugs including biologics. Based on the IORRA data, 20% of RA patients are now receiving any kinds of biologics and over 50% of all patients are in clinical remission. On the other hand, use of expensive biologics has large impact on both national medical cost and family finances of patients. It is quite important to consider the cost-effectiveness of biologic use by scientific methods including pharmacoeconomical approach. We have conducted a pharmacoeconomical analysis using IORRA database to compare the cumulative lifelong cost and Quality Adjusted Life Years (QALY) in methotrexate (MTX) group and biologics group. As the result, average cumulative lifelong cost and average QALY was 24,264,393yen and 8.292 in MTX group and 34,853,554 yen and 11.066 in biologics group. The incremental cost-effectiveness ratio (ICER) was calculated to be 3,817,871yen. In Japan, the cut off of ICER for the cost-effectiveness of new treatment is considered to be 5,400,000 yen. Thus, our results demonstrated that the ICER was lower than this level, and biologic use is considered to be cost-effective. Furthermore, sensitivity analyses demonstrated that earlier use of tocilizumab in biologics group effectively decrease the ICER and use of biologics to the patients who is capable to restore the labor productivity has advantage to decrease ICER. It is time to consider the optimal use of biologics from the perspective of pharmacoeconomics. RA is a chronic disease whose long term outcome of the disease has large impact on both patients and society. Even if short-term outcomes of biologics use might be less cost-effective, long-term outcome of biologics use is considered to be sufficiently cost-effective. Pharmacoeconomical studies of RA treatment will be discussed in this seminar.

### LS30-2

#### Healthcare cost and medical insurance system for patients with rheumatoid arthritis in Japan

Hiroaki Matsuno<sup>1,2</sup>

<sup>1</sup>Matsuno Clinic for Rheumatic Diseases, Toyama, Japan, <sup>2</sup>Institute of Medical Science, Tokyo Medical University, Tokyo, Japan

Conflict of interest: None

Rheumatoid arthritis is a prevalent condition associated with pain, joint destruction. Biological agents are very useful treatment for active rheumatoid arthritis, but there are still many problems which must be solved, including their high cost and the problem of adverse reactions such as infections. Direct healthcare costs of biological agent treatments are 25 times higher than average costs for conventional DMARDs treatment patients. The majority of patients desire that medical expenses is less than 10,000 yen per month, but the monthly cost of many biological agents is 30,000 yen or more. This expensive self-payment medical costs are caused by insurance system in Japan. All of Japanese patients unlike the Americans have medical insurance. Ratio of shared medical benefit payable by the patient is about 30% in Japan and Korea. However the other OECD countries does not need a patient self-pay medical costs. Medical costs of biological agents has been expensive, but healthcare fee that doctors receive has been low. From 2014, this inappropriate healthcare cost gets even worse. Outpatient chemotherapy and self-injection administrative fee was reduced. Hence healthcare fee decreased and income of doctor was more reduced. The serious infection is sometimes caused by a biological agent treatment, therefore, the physician must pay great attention. Although this treatment is very delicate, healthcare fee is not enough. We must correct this unfair state of biological agent treatment administrative fee.

### LS31

#### **Positioning of Igaratimod in patients with rheumatoid arthritis based on a report covering 24 weeks of an all-patient investigation**

Naoki Ishiguro

Department of Orthopaedics and Rheumatology, Nagoya University, School of Medicine, Nagoya, Japan

Conflict of interest: Yes

MTX is currently an “anchor drug” for the early treatment of rheumatoid arthritis (RA). Even if treatment is started at a sufficient dose of MTX, 20 - 40% of patients do not respond well. If the treatment goals are not achieved, the concomitant addition of other DMARDs or biological preparations may be required. Igaratimod (IGU) is a new oral anticoagulant disease-modifying anti-rheumatic drug (DMARD) that a domestic phase III study has shown to be noninferior to salazosulfapyridine when provided as monotherapy. Its concomitant effect with MTX has been verified in patients not responding to MTX, and has been approved in the context of the current treat-to-target (T2T) approach. An all-patient investigation of IGU was performed after its launch in September 2012, in which the patients' background, status of combination with DMARDs, continuation rate, as well as status of occurrence of adverse reactions and risk factors as the principal items of investigation, and the disease activity and improvement rating in terms of safety and efficacy for elderly, low-body-weight patients and the presence or absence of combination of MTX were analyzed in 2737 patients enrolled before April 14, 2013. We report the statistical results over 24 weeks of the all-patient investigation. We also report the result of a cohort study in subjects in a multicenter study organized by Nagoya University's Department of Orthopedic Surgery (TBCRplus). In this lecture, we will discuss the positioning of IGU from the results of the all-patient investigation and TBCRplus and show the role of low-molecular-weight DMARDs in RA treatment.

### LS32

#### **Difficulties in diagnosis and treatment of pulmonary hypertension associated with connective tissue diseases: lessons and discussions from our cases**

Yoshioki Yamasaki

Rheumatology and Allergology, St. Marianna University School of Medicine

Conflict of interest: Yes

Pulmonary hypertension (PH) is one of the life-threatening organ involvements complicated in connective tissue diseases (CTD). Roughly 10 % of the patients with systemic sclerosis, systemic lupus erythematosus (SLE), and mixed connective tissue disease (MCTD) suffer from PH. Al-

though less frequently, PH is seen in almost all CTD like primary Sjögren syndrome, myositis, and systemic vasculitis such as Takayasu arteritis. Evaluation of the underlining CTD is important to decide treatment strategies of PH-CTD. Right heart catheterization is mandatory for the diagnosis of PH because pre-capillary or post-capillary PH may attribute the cause of PH. It is of note that misdiagnosis of pre- and post-capillary PH may occur if values of mean pulmonary arterial pressure (mPAP) and pulmonary artery wedge pressure (PAWP) were simply applied to definition of PH without considering the underlining conditions. Additionally, misuse of pulmonary vasodilators may lead to deterioration of heart failure due to increase in preload if patients have post-capillary PH. We will present such cases in this session. Some favorable outcomes have been reported on the use of immunosuppressive agents against PH due to SLE or MCTD. Careful evaluations of individual CTD-PH patients by Rheumatologists is required regarding the indications of immunosuppressants. In this session we will also discuss the clinical characteristics of the CTD patients who have response to immunosuppressants including PH associated with systemic sclerosis.

### LS33

#### **Best use of biologics in maintenance of remission in rheumatoid arthritis: consideration for immunogenicity**

Masataka Kuwana

Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine

Conflict of interest: Yes

Over the past 10 years, treatment algorithm of rheumatoid arthritis (RA) has made remarkable progress. Updated recommendations for achieving optimal therapeutic outcomes in RA include early clinical remission as the primary target for treatment, and frequent adjustment of drug therapy is required until completion of the desired treatment target. It has been widely recognized that introduction of biologics has enabled us to achieve this treatment goal with ease. However, it is more important to sustain clinical remission for a long period to stop progression of joint damage and impaired activity of daily living. The most frequent cause of attenuation of efficacy during biologic treatment is production of anti-drug antibodies, which recognize complementarity-determining region, mouse-derived portion, or neo-epitopes produced by fusion of unrelated proteins. Anti-drug antibodies are capable of reducing efficacy of biologics, by competitively binding to antigen-recognition site and/or by facilitating clearance of the biologics and resultant decline in the trough levels. In addition, immune complexes formed by biologics and anti-drug antibodies often induce skin and systemic immune reaction, leading to halt of the biologics. Factors affecting production of anti-drug antibodies include disease activity; genetic predisposition; history of anti-drug antibody production; molecular structure, dosage, interval, and route of biologic administration; and concomitant use of immunosuppressants such as methotrexate. Multidisciplinary approach considering these factors are essential to achieve long-term remission in RA patients.

## Evening Seminar

### ES1-1

#### Intravital bone imaging dissecting the 'real' mode of actions of anti-bone resorptive drugs

Masaru Ishii

Graduate School of Medicine & Frontier Biosciences, Osaka University

Conflict of interest: Yes

During the last decade, multi-photon fluorescent microscopy has launched a new era in the field of biology. By using this advanced imaging technique we have established a new system for visualizing in situ behavior of a diversity of living cells within intact tissues and organs. Among them, we succeeded in visualizing the various dynamic phenomena within bones, a mysterious organ where various kinds of hematopoietic and immune cells are produced and functioning although poorly analyzed by conventional methodology such as histological analyses with decalcified bones. Especially we have focused on the behavior of osteoclast, a kind of specialized macrophage contributing to physiological bone remodeling as well as to bone destruction in arthritis and osteoporosis, and have been revealing novel mechanisms controlling migration and function of osteoclasts in situ. In this presentation, I will show in vivo cellular dynamics in bone and inflammatory systems, and also present our latest data showing the real mode of actions of anti-bone destructive drugs.

### ES1-2

#### The reconsideration of the utility of bisphosphonates for osteoporosis

Satoshi Soen

Department of Orthopaedic Surgery and Rheumatology, Nara Hospital, Kinki University School of Medicine

Conflict of interest: Yes

The drug that fracture preventive effect is proved for vertebral, non-vertebral and hip fracture in post-menopausal osteoporosis, vertebral fracture in male osteoporosis and glucocorticoid-induced osteoporosis is two bisphosphonates including alendronate and risedronate. In addition of preventing effect of hip fracture in clinical trials, the decrease of the incidence of hip fracture in Western countries and Australia is confirmed with appearance and increase of the quantity of prescription of these bisphosphonates. Furthermore, the vital prognosis improvement effect with the bisphosphonates was also found, and the association with bisphosphonates and the decreases in cardiovascular events, the onset of malignant tumors, and the infection are suggested. A dose of alendronate and risedronate is half a dose in Japanese compared with overseas, but the preventive effect of contralateral hip fracture by risedronate after the hip fracture was shown by an observational study of our country. Whereas association with osteonecrosis of the jaw and the atypical femoral fracture was pointed out with the long term administration of bisphosphonates, and FDA revises the attached document in 2013, as for "The optimal duration of use has not been determined. The safety and effectiveness of bisphosphonates for the treatment of osteoporosis are based on clinical data of three to five years duration. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis. Patients at low-risk for fracture should be considered for drug discontinuation after 3 to 5 years of use. Patients who discontinue therapy should have their risk for fracture re-evaluated periodically". Multiple thought is shown about a condition of the withdrawal of bisphosphonates, and a common point is that there is no prevalent fracture and that bone mineral density of the hip escapes from an osteoporotic region.

### ES2-1

#### The Impact of Immunological Cells on Rheumatoid Arthritis by IL-6 Signal Inhibition~ Considering Future RA Treatment Perspective ~

Tsutomu Takeuchi

Division of Rheumatology, Department of Internal Medicine, School of Medicine, Keio University

Conflict of interest: Yes

The continuing research on the mode of action of each biologic is one of the issues which should be developed in order to understand the RA pathogenesis with more than seven biologic agents available in Japan. Our research has shown that it is important for RA patients (pts) to suppress IL-6 production, even if for pts treated with TNF inhibitors, it can suggest that IL-6 signaling is key player for RA in autoimmune disease. Tocilizumab (TCZ) significantly improves disease activity and suppresses progress of joint destruction. Our detailed research described that TCZ is somewhat different from other biologic agents in changes in biomarkers. Interestingly, TCZ raised the level of bone formation markers such as osteocalcin and BAP, while it lowered the bone resorption markers. What is called, "Uncoupling" effect was found in pts treated with TCZ. We consider that "Uncoupling" effect generated by TCZ is one of the possible mechanism of blocking bone destruction. We also investigated the relationship between disease activity and changes of PBMCs in RA pts treated with TCZ and found that regulatory T cells in CD4 positive cells and activated regulatory T cells increased, whereas memory B cells and classical monocytes were decreased by TCZ. We also confirmed that TCZ affected immunological cells, and changes of regulatory T cells were related with the regulation of disease activity on RA. RA pathogenesis could be elucidated in considerable detail through our translational research. TCZ was added as a 1<sup>st</sup> line therapy in EULAR recommendation and ACR guideline in the last two years. The positioning of IL-6 signal inhibition is established worldwide and it would be certainly worthy of the use for physicians under the daily setting care. However, how we optimize TCZ treatment remains the matter of research for further development. In this symposium, I will discuss the research overview we have been conducting, taking into consideration of the issues for future RA treatment.

### ES2-2

#### Can we taper or even stop DMARD treatment in RA?

Georg Schett

Department of Internal Medicine 3, University of Erlangen-Nuremberg, Germany

Conflict of interest: None

Due to improved therapeutic management a steadily increasing number of rheumatoid arthritis (RA) patients reach stable remission of disease. Data on withdrawal of medication after sustained remission are limited, though it is important for economic and safety reasons. The RETRO study represents a real-life study addressing different strategies of reduction of DMARD therapy in RA patients in stable disease remission. The aim of the study was to evaluate the possibility of tapering and even discontinuation of DMARD therapy in RA patients in stable long-lasting remission and to determine predictors for recurrence of disease. RETRO is a phase 3, multicenter, randomized, controlled, open, prospective, parallel-group trial. Patients, fulfilling the ACR/EULAR 2010 criteria for RA with disease history of  $\geq 12$  months, were enrolled into the study if they were in clinical remission (DAS28-ESR  $< 2.6$ ) at stable dose of DMARDs for more than 6 months. Patients on  $\geq 1$  conventional and/or biological DMARDs were included and randomized into three treatment arms: Arm 1 (control group) was continuing full-dose conventional and/or biological DMARD treatment for 12 months; arm 2 was reducing the dose of all conventional and/or biological DMARD treatment by 50% for 12 months and arm 3 was reducing the dose of all conventional and/or biological DMARD treatment by 50% for 6 months before entirely stopping DMARD. In case of recurrence of disease (DAS  $> 2.6$ ) the original therapy was restarted. 101 patients (61.4% females, 60% ACPA positive, 63% RF positive; 37.6% biologic therapy, 80.2% MTX, 7.9% other DMARDs) finished the one year endpoint. Of 101 patients, 66.3% were still in remission at 12 mo. Significantly more patients flared in reduction arm 2 (38.9%,  $p=0.036$ ) and arm 3 (51.9%,  $p=0.003$ ) compared to control arm 1 (15.8%), while there was no significant difference between the two reduction arms ( $p=0.443$ ). With multivariate logistic regression ACPA positivity ( $p=0.03$ ) and treatment reduction (group 2a  $p=0.01$ , 2b  $p=0.003$ ) were detected as predictors for flares. Sex, disease duration, remission duration, age, RF, biologic DMARD and remission depth (defined by fulfilling Boolean remission criteria yes/no) failed to predict recurrence of disease in this study. This study is a prospective real life treatment strategy study investigating the effect of reduction and discontinuation of DMARD therapy in RA patients in stable remission. Interest-

ingly remission depth and disease duration at baseline did not predict the recurrence of disease and also the use of biological DMARD therapy at baseline did not influence flare rates. Presence of ACPA but not RF was the only predictor for recurrence of disease. The data indicate that treatment reduction and even discontinuation is feasible in a subset of RA patients in stable remission.

### ES3-1

#### Current Status and Future Scope of RA treatment with Biologics in Japan

Kazuyoshi Saito

The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health

Conflict of interest: Yes

Since the approval of infliximab in 2003, seven biologics have been approved for use in Japan and are now essential treatment options for rheumatoid arthritis (RA). In the early 2000s, Japan lagged behind other countries with respect to approval of new therapeutic options for RA. However RA treatment in Japan has already caught up with to other countries by several factors as follows, (i) infliximab (and other new agents) all-patient post-marketing surveillance led by JCR, (ii) new biologic agent (anti-IL-6R antibody) approved firstly in Japan and now widespread to the countries, (iii) several efficacious csDMARDs (bucillamine and tacrolimus) are approved and widely used for RA in Japan. In this lecture, I will review the changes in treatment regimens involving biologics in Japan over the past decade by evaluating the results of multicenter studies performed in Japan, as well as the treatment outcome analysis of 2200 biologics-treated patients at our institute, the University of Occupational and Environmental Health. I am particularly interested in discussing how therapeutic results changed before and after 2009, when infliximab was approved for dose increase and shortening of intervals. I believe that the findings from our institute in three phases - immediately after initial approval of infliximab, before approval of dose increase and shortening of intervals, and after approval thereof - may offer several suggestions with regard to the optimal use of biologics including infliximab. In addition, given that the “treat to target” strategy for RA is becoming more widely adopted, I will discuss the patient benefit arose from infliximab treatment optimization. I will also touch on the future prospects of RA treatment with biologics in Japan in light of the recent wave of reports of therapeutic results from novel targeted small molecule drugs.

### ES3-2

#### Clinical updates in RA treatment

Tom W Huizinga

Leiden University Medical Center, Leiden, The Netherlands

Conflict of interest: None

Appropriate drug treatment in Rheumatoid Arthritis (RA) can improve outcome dramatically. Strategy studies how to use medication best involve intensifying medication as long as low disease activity is not achieved. Now, we focus on opportunities for tapering and discontinuing medication when the target is achieved. The “BeSt” -study compares 4 treatment strategies: 1. Sequential monotherapy, 2. Step up to combination therapy (both starting with methotrexate (MTX) monotherapy), 3. Initial combination therapy with MTX, sulfasalazine and prednisone and 4. Initial combination therapy with MTX and infliximab. Treatment adjustments involving dose increases, drug changes or expansion to combination therapy based on three-monthly Disease Activity Score (DAS) measurements, with a target of  $\leq 2.4$ . If this was achieved for 2 consecutive evaluations, treatment was tapered (combinations to monotherapy, monotherapy to maintenance dose). Prednisone and infliximab (either as part of initial treatment or as delayed treatment after failure on earlier therapies) were always tapered first. 77/120 of patients who started initial infliximab were able to discontinue infliximab, whereas 27/109 of patients who started delayed infliximab in arms 1-3 could discontinue infliximab. After discontinuation of infliximab, 16 of 27 patients in arms 1-3 and 34 of 77 patients in arm 4 suffered a DAS flare  $>2.4$  and had to restart treatment. Median time without infliximab treatment was 17 (IQR

3-47) months, and 29 of the 61 patients who needed to restart had been at least 1 year without infliximab. Restarting infliximab resulted in DAS  $\leq 2.4$  in all patients. Presence of shared epitope, smoking, and a long treatment with infliximab were independent predictors of infliximab restart. In conclusion these data on infliximab discontinuation suggest that in all clinical situations it is possible to discontinue if infliximab in a considerable proportion of patients

### ES4-1

#### Clinical significance of antibody production in patients with rheumatoid arthritis

Takao Fujii

Department of the Control for Rheumatic Diseases, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Conflict of interest: Yes

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by erosive arthritis. It is, therefore, important for RA diagnosis to detect serum autoantibody (auto Abs) in clinical practice. In the 2010 ACR/EULAR classification criteria for RA, the item of serology including rheumatoid factors (RF) and anti-citrullinated protein/peptide Abs (ACPA, usually determined as anti-cyclic citrullinated peptide Abs) occupies 30% among all the items, so both Ab testing is required for RA diagnosis. These Abs, especially high titer of Abs, are also important as a prognostic factor for bone injury. Because T cell-targeting agent such as abatacept appears to be effective in ACPA-positive than in -negative patients, ACPA positivity is one of the useful markers for biological disease-modifying anti-rheumatic drug (bDMARD) treatments. Anti-nuclear antibody (ANA) determination should be performed for a differential diagnosis of RA. Indeed, lower titer of ANA can be observed also in sera from RA patients, but high titer of ANA ( $\geq \times 320$ ) might indicate other connective tissue disease (e.g., systemic lupus erythematosus) or overlap syndrome with RA. TNF inhibitors are one of the possible inducers of lupus-like syndrome, so rheumatologists should take care of ANA positivity in non-erosive arthritis patients. We reported that the efficacy of infliximab was markedly reduced in RA patients with ANA-positive and/or an increasing titer of ANA during disease course. Finally, immunogenicity, which usually means the genesis of neutralizing Abs against bDMARDs, has been known as harmful reactions in RA. The development of immunogenicity in RA patients treated with bDMARDs must be associated with a negative impact not only on their efficacy but also on cost effectiveness. In this lecture, clinical significances of those Abs associated with RA will be discussed.

### ES4-2

#### The role the biologics have been playing in RA treatment and their future prospects

Lars Klareskog

Rheumatology Unit, Department of Medicine, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

Conflict of interest: None

Medicines that we call “biologics” have been developed as a consequence of both increased understanding of pathogenic pathways in rheumatic diseases, and as results of progress in biotechnology that has enabled the development of drugs that specifically can interfere with these pathways using molecules (biologics) that in some way mirror molecules that are or can be produced by an individual’s own molecular machinery. Rheumatology, and in particular RA, was not the field where such drugs were first used (insulin, for example is a prototype of a biological), but the introduction of biologics in rheumatic diseases, in particular RA provided a major shift of thinking and practice in drug development and use, not only in rheumatology, but also in many other fields of medicine. The current lecture will discuss how biologics in rheumatology were developed introduced and developed into its current standing, and which features of drug development, implementation and evaluation that have been critical for the development we have seen. The lecture will also discuss the challenges to the use of current biologics from recent comparative effectiveness studies, and discuss challenges for future developments of different classes of biologics, with the perspective provided from the in-

creasing understanding of molecular pathways that are involved in different subsets of disease in RA as well as in other rheumatic conditions.

### ES5-1

#### Role of Antibody Agents in Osteoporosis

Hiroaki Matsuno<sup>1,2</sup>

<sup>1</sup>Matsuno Clinic for Rheumatic Diseases, Toyama, Japan, <sup>2</sup>Institute of Medical Science, Tokyo Medical University

Conflict of interest: None

Osteoporosis medication can be divided into three broad categories: 1) drugs which increase the absorption of calcium by the intestines (such as vitamin D and calcium (Ca)); 2) bone resorption inhibitors (such as bisphosphonates (BP), SERMs, calcitonin, and the anti-RANKL antibody); and 3) osteogenesis promoters (such as PTH). A large number of clinical trials have been conducted for BP and there is a high level of evidence. The mechanism of action for BP is based on its high adsorption; this high adsorption allows BP to break into the site of osteoclasts (OC) activity and eventually drive OC into apoptosis while controlling the function of OC. The anti-RANKL antibody is also a bone resorption inhibitor; however, its mechanism of action differs from that of BP. The anti-RANKL antibody prevents mature OC from being produced by competitively blocking the binding of RANK on osteoclast precursor cells and RANKL secreted by osteoblasts. BP has a good effect on the augmentation of cancellous bone mass along with bone mineral for vertebrae and hip joints, but has a poor effect on the augmentation of cortical bone mineral for distal radii. In contrast, the anti-RANKL antibody works well on cortical bones and augments bone mineral. In addition to this, the anti-RANKL antibody's effect on the augmentation of bone mineral has been proven to last for as long as the treatment is continued. Many bio agents have been used to treat rheumatoid arthritis and within those agents, a fully human antibody produced from Xeno Mouse is regarded to have high safety and product stability. The anti-RANKL antibody is believed to be highly safe as it is also prepared by using this transgenic method. The anti-RANKL antibody—is believed to have the potential to contribute to the improvement of the treatment continuity rate.

### ES5-2

#### Clinical application of anti-RANKL antibody

Sakae Tanaka

Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo

Conflict of interest: Yes

Osteoclasts are multinucleated giant cells primarily responsible for bone resorption. Osteoclasts are differentiated from monocyte/macrophage-lineage precursor cells in the presence of receptor activator of NF- $\kappa$ B ligand (RANKL) and macrophage colony-stimulating factor. A number of studies have shown that RANKL-RANK pathways play essential roles in the pathologic bone resorption such as osteoporosis, rheumatoid arthritis, cancer bone metastasis and periodontal diseases. Denosumab, a fully human IgG2 monoclonal antibody that binds human RANKL with a high affinity, potently suppresses osteoclast development and reduces bone resorption. In a study of postmenopausal osteoporosis patients (FREEDOM), denosumab significantly reduced the risk of new vertebral fractures at 3 years by 68%, non-vertebral fractures by 20% and hip fractures by 40% relative to placebo. To examine the anti-fracture efficacy and safety of denosumab (60 mg subcutaneous injection every 6 months [Q6M]) in Japanese patients with primary osteoporosis, a randomized, double-blind, placebo-controlled trial with an open-label referential arm was conducted (DIRECT trial). Denosumab reduced the risk of new or worsening vertebral fracture, with incidences of 3.6% in the denosumab group and 10.3% in the placebo group in 24 months without increasing the risk of adverse events of interest. These results suggest that anti-RANKL therapy is effective in reducing osteoporosis fractures.

### ES6-1

#### How do you manage serum MMP-3 as a useful tool in the treatment evaluation of the rheumatoid arthritis?

Yosuke Hattori

Department of Orthopaedic Surgery and Rheumatology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan

Conflict of interest: Yes

The treatment target in rheumatoid arthritis (RA) is remission, and it is necessary to judge disease activity and a drug effect appropriately, and to practice tight control in RA. Serum matrix metallo-proteinase-3 (MMP-3) is considered that specificity is more useful for RA for an index of the disease activity highly than CRP. We examined the usefulness as the remission prediction factor by using multicenter study data in Tsurumi Biologics Communication Registry whether serum MMP-3 could become the index of the remission prediction in biological treatment for RA. If serum MMP-3 at 4 weeks was improved 40% after ADA introduction, the probability to achieve DAS remission rate at 52 weeks was predicted with 47%. On the other hand, if serum MMP-3 at 4 weeks was not improved 40%, the probability not to achieve DAS remission at 52 weeks was 83%, and it was considered to review the treatment policy at an early stage. The improvement of serum MMP-3 at 4 weeks participates in the remission at 52 weeks in comparison with the improvement of CRP, and the remission rate at the time of treatment evaluation become higher when the serum MMP-3 levels decreases in addition to the lowering of CRP levels. By the evaluation that combined CRP with serum MMP-3, the effectiveness may be predicted more. Furthermore, treatment continuation may be predicted by combined evaluation of serum MMP-3 and CRP at 4 weeks. RA treatment was dramatically improved by an appearance of biologics. Because the therapeutic response differs in individual patients, by inspection indicators that can predict remission earlier, we will enable good communication with the patient on to continue the expensive treatment. In future, evidence from Japan for utility for measuring serum MMP-3 in the real clinical is expected to be built.

### ES6-2

#### MMP-3 and imaging in the treatment for rheumatoid arthritis

Isao Matsushita, Hiraku Motomura, Tomoatsu Kimura

Department of Orthopaedic Surgery, Faculty of Medicine, University of Toyama

Conflict of interest: Yes

In patients with rheumatoid arthritis (RA), proliferating synoviocytes in the joints produce various inflammatory cytokines and matrix metallo-proteinases (MMPs). Activated MMP-3 degrades the extracellular matrix and this leads to destruction of cartilage. Therefore, the serum level of MMP-3 is considered to be a predictor of the progression of joint destruction. We investigated the association between the serum MMP-3 level and joint destruction in patients with RA treated with tacrolimus (TAC). When 27 patients with RA were treated with TAC and followed for 2 years, the serum MMP-3 level showed a significant decrease after the initiation of TAC therapy. In addition, the serum MMP-3 level after 1 year of treatment with TAC showed a significant correlation with DmTSS after 1 year ( $r = 0.39$ ,  $P < 0.05$ ) and with DmTSS after 2 years ( $r = 0.53$ ,  $P < 0.01$ ). This suggests that the serum level of MMP-3 is closely associated with joint destruction. We also investigated the association between damage to large joints and the serum level of MMP-3 in RA patients based on data accumulated by the ARASHI study group. Ten large joints (the bilateral shoulder, elbow, hip, knee, and ankle joints) were examined in 64 patients with RA and the total ARASHI score was calculated. At 1 year, we compared the serum MMP-3 level between subjects in whom the change of the total ARASHI score was  $\geq 1$  (progression group, 18 patients) and subjects in whom the change of the total ARASHI score was  $< 1$  (non-progression group, 46 patients). The mean serum level of MMP-3 at 1 year in the non-progression group was significantly lower in that in the progression group. Thus, reducing the MMP-3 level is also important with regard to preventing the progression of large joint destruction. In this seminar, I would like to talk about the significance of measuring the serum MMP-3 level in RA patients from the viewpoint of joint destruction.



## ES7-1

### How can we select the second biologics for the treatment of rheumatoid arthritis?

Tatsuya Koike

Search Institute for Bone and Arthritis Disease, Shirahama Foundation for Health and Welfare, Wakayama, Japan

Conflict of interest: Yes

Ten years have passed from the start of biologics (BIOs) era for rheumatoid arthritis (RA) treatment in Japan. At the present time, 7 BIOs are available and the lineup is almost same to foreign countries. BIOs are used as a usual treatment for RA now. The continuation rates of BIO in clinical setting are not so high. As the reasons for discontinuation of BIO, there are several possibilities such as the discontinuations by adverse events by BIO, by the economic reason, by low clinical effects, by the attenuation of the clinical effects. Of course it should be the best way to use first BIO effectively for a long term. However, it is an important issue to select what kinds of second BIO or not to select. For every above-mentioned discontinuation reason, let's think about the next choice. The harmful phenomenon varies, but the second BIO choice is relatively easy if it is the case of injection site reaction. In the case of an infectious disease, it will be available to use same BIO if we can completely bring it under control. However, logical choice should be required in the case of a malignant tumor as showing in the new guidelines by American College of Rheumatology (ACR). It deviates from the main street of the biologic treatment to select cheaper BIO for the discontinuation by the economic reason of patients. However, biosimilars might be considered in future. When BIO does not show any effect from the beginning, there might be an error in setting a target or relative shortage of BIO against disease activity. In the case of subcutaneous administration of BIO, the influence of the body weight should be considered. When the effect that existed at first attenuates during the treatment, the target was not wrong and so there might be a lack of suppression of inflammation or a appearance of neutralizing antibody against BIO. In this talk, I will show a personal opinion while considering a new ACR guideline for the treatment of RA or the data from past clinical studies.

## ES7-2

### Therapeutic evaluation and alteration of biological agent

Hideto Kameda

Toho University Ohashi Medical Center, Tokyo, Japan

Conflict of interest: Yes

Therapeutic outcome of biological agents in patients with rheumatoid arthritis (RA) may be determined by the choice of biological targets/agents and their dosing regimen. Unexpectedly, according to recent clinical trials including head-to-head trials and those enrolling TNF-IR (inadequate response to anti-tumor necrosis factor) patients, all the available biological agents with concomitant methotrexate (MTX) have shown comparable effectiveness in the similar patient group, and TNF-IR patients tend to be refractory to both other anti-TNF agents and biological agents with different mode of action from anti-TNF. Based on those evidences, recent recommendations and guidelines for RA treatment do not indicate the priority of specific biological agents. Therefore, it would be appropriate to select biological targets/agents chiefly based on safety profiles of the patient, and to administer maximum available dose of the agents in the remission induction phase in order to avoid insufficiency. Both 50 mg and 100 mg of monthly golimumab injection have been approved in Japan for RA patients receiving MTX. Thus, we can start with 50 mg of golimumab in view of health economics and increase to 100 mg on the following injection for patients showing lack of efficacy. At the same time, it may be reasonable to start with 100 mg of golimumab for seemingly refractory (TNF-IR, for example) patients, and decrease to 50 mg soon after recognizing sufficient clinical response. Hopefully, this seminar will be helpful in the consensus development on the appropriate use of biological agents by discussing about the decision of treatment failure and its underlying mechanisms as well as the unmet need in the currently approved dosing regimen, based on the available evidences regarding the importance of the measurement of blood concentration of cytokines and biological agents.

## ES8-1

### Lesson from TNF blockade – how to do even better

Iain McInnes

Institute of Infection, Immunity and Inflammation, University of Glasgow, Scotland, UK

Conflict of interest: Yes

The advent of biologic therapeutics in general, and TNF inhibition in particular remains one of the seminal advances in the treatment of inflammatory rheumatic diseases. In this lecture I shall reflect upon the success of TNF inhibition with a view to further optimising our treatment approach to rheumatoid arthritis (RA). Thus, I will: 1. Revisit the rationale for TNF targeting in RA and consider its position as the most commonly used first line biologic agent in current practice. I shall integrate factors including pathogenetic rationale, effect on clinical disease activity, radiographic progression, safety and impact on common co-morbidity in this discussion. 2. Thereafter I shall consider why TNFi, and indeed probably all cytokine inhibitors fail in the context of both primary and secondary failure? 3. Given such therapeutic failures, how do other cytokines offer further opportunities in RA? Herein I shall briefly review the wider cytokine network in RA synovitis and beyond with a view to supporting a subsequent clinical trial overview by Dr Yamaoka. 4. Finally I shall give consideration to approaches that might enrich for response and reduce therapeutic failure. Together these thoughts will contextualize the success of current TNF targeting approaches with a view to optimizing the benefits that we can hope to achieve in future.

## ES8-2

### TNF Inhibitor failed; What's Next?

Kunihiro Yamaoka

Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine

Conflict of interest: Yes

TNF inhibitors (TNFi) are often used as first-line biologics in the treatment for RA, but we often face in discontinuing because of primary, secondary failures and adverse events. In the case of primary failure, there is no question to choose tocilizumab (TCZ) or abatacept (ABT), those with different modes of action from TNFi. However, when discontinuation is due to adverse events or secondary failure, it becomes controversial and there are various opinions on which biological agent is suitable as next the treatment. This seminar will focus on this matter and discuss on "What's next" depending on the existing evidence. GO-AFTER study, in which golimumab (GLM) was administered to patients previously treated with other TNFi, significant improvement was observed with ACR20, 50 and 70 response rate at 24 weeks (combined 50 mg with 100 mg) compared to placebo (PLB) (40.8%, 20.9% and 11.4% vs. 14.6%, 3.9% and 2.9%). On the other hand, in RADIATE study with TCZ, to which patients with similar background were enrolled, ACR20 response rate at 24 weeks was significantly higher in TCZ than in PLB (30.4% of TCZ 4 mg/kg and 50.0% of TCZ 8 mg/kg vs. 10.1% of PLB), and both ACR50 and 70 response rates showed significantly higher in TCZ 8 mg/kg. Additionally, in ATTAIN study with ABT, ACR20, 50 and 70 response at 24 weeks were 50.4%, 20.3% and 10.2% in ABT compared to 19.5%, 3.5% and 1.5% in PLB, respectively. Based on these results, similar efficacy can be expected with these drugs in patients who discontinued TNFi. Even though deciding the next biologics is difficult after TNFi, one may prefer a drug with lower immunogenicity if the onset of anti-drug antibody is associated with discontinuation. On that note, GLM is known with low incidence rate of anti-drug antibody at 52 weeks; 3.9% in GO-MONO and 0.0% in GO-FORTH study. In this seminar, treatment strategy for patients who have discontinued TNFi will be introduced and overview the recent treatment strategies.

## ES9-1

### What is next important for clinical practice?

Josef S. Smolen

Medical University of Vienna, Austria

Conflict of interest: Yes

The current therapeutic landscape allows for almost two thirds of our rheumatoid arthritis (RA) patients to reach the well-established treatment targets, remission or low disease activity. However, when sitting in front of a patient it is frequently difficult to decide about the specific therapeutic approach. In this respect, EULAR recommendations are helpful as a guidance toward best use of available agents, but it is still impossible to predict who will respond to which agent best (or to which of them not at all) or who will profoundly respond to a particular drug. This contrasts many non-rheumatological diseases, such as in the field of hematology and oncology. Therefore predictors of response must still be sought also for RA to allow a more precisely targeted treatment approach. On the other hand, many patients do achieve the treatment target and decisions have to be made how to best adapt treatment in this situation. It appears that in established RA it is difficult to stop biological therapy, since a large majority of the patients will flare within few weeks to one year. On the other hand, dose reduction or expansion of intervals between doses appears to be a viable option. However, in early disease the hope for a window of opportunity continues to exist. If it really exists, one could apply induction regimens using early intensive therapies followed by withdrawal of drugs. The pros and cons regarding the window of opportunity hypothesis will be discussed.

### ES9-2

#### Early intervention by synthetic and biological DMARDs, maintenance of remission and subsequent biological DMARD-free remission for the treatment of rheumatoid arthritis

Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational & Environmental Health, Japan

Conflict of interest: Yes

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by destructive synovitis with concurrence of organ disorders. Joint damage progresses from the early stage, which causes irreversible physical dysfunction. Thus appropriate diagnosis and therapy at the early stage are important in the treatment. The recent emergence of synthetic DMARDs and biological DMARDs has dramatically improved the outcome of RA treatment. In response to these changes, ACR and EULAR successively announced classification criteria, therapeutic recommendation and remission criteria. JCR also announced guidelines for RA treatment in 2014, in which the therapeutic goals are defined as not only amelioration of clinical symptoms but also improvement of long-term prognosis, especially prevention of physical dysfunction. Appropriate use of synthetic and biological DMARDs targeting TNF has increased the likelihood that the therapeutic goals recommended by the guidelines can be achieved. Furthermore, ANOUVEAU study has clarified that shorter disease duration before starting adalimumab leads to better clinical response and work related outcomes in Japanese patients with RA. We also need to create the therapeutic strategies for the long-term maintenance of remission in order to keep structural remission, functional remission and social remission. On the other hand, HOPEFUL study indicates that more than half of early RA patients could discontinue adalimumab after obtaining remission. However, fewer patients successfully discontinued adalimumab in established RA in HONOR study, but deep remission at the discontinuation is a key factor to keep the treatment holiday of adalimumab. But, such an intensive treatment with adalimumab would have the potential of reducing drug-induced adverse effects and reducing long-term medical costs. I will discuss the importance of early therapeutic intervention, a good long-term outcome and the possibility of treatment holiday of biological DMARDs

### ES9-3

#### Role of MTX in strategic treatment for RA - evidence from recent findings -

Tsutomu Takeuchi

Division of Rheumatology, Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan

Conflict of interest: Yes

Therapeutic goals for rheumatoid arthritis (RA) should be achieved

at an early stage by early diagnosis and appropriate intervention. The various clinical studies demonstrate that delay of therapeutic intervention negatively affects the long-long term outcome, and early and tight control of disease activity in recent treatment algorithm. The anchor drug for therapeutic intervention is methotrexate (MTX), which is recommended as the first-line therapy. Currently, it is approved to increase the dose of MTX to 16 mg/week at a maximum in Japan. In usual clinical practice, however, the dose cannot be increased to the maximum level in not a few patients partly because of the influence of adverse reactions, such as gastrointestinal symptoms. On the other hand, MTX can achieve clinically great effects in some patients even at a dose lower than 16 mg/week. The optimum dose of MTX to provide a good balance between efficacy and safety varies among individual patients, and definite criteria have not been established yet. In addition, for cases in which MTX monotherapy is not sufficient and a biological drug, such as a tumor necrosis factor (TNF) inhibitor, needs to be added to the therapy, sufficient evidence has not been obtained about the optimum dose of MTX when it is used in combination with each of the biological drugs. In these situations, we continue to research the optimum dose of MTX for Japanese patients in our department. In this seminar, I will focus on the aforementioned importance of early therapeutic intervention by using the data from several studies. The optimum dose of MTX for RA treatment should be discussed by the subjective measures such as methotrexate-polyglutamate (MTX-PG) within the cells. In this regard, recent findings not only from overseas (CONCERTO study and MUSICA study), but also from Japan (MAGIK study) will be remind, and discussed.

### ES10

#### Surgery of Rheumatoid Hand 2015

Takashi Masatomi<sup>1,2</sup>

<sup>1</sup>Society for Surgery of the Rheumatoid Hand, <sup>2</sup>Upper extremity Surgery Center, Department of Orthopedic Surgery, Yukioka Hospital, Osaka, Japan

Conflict of interest: Yes

It becomes the 17th this year that this meeting for the study repeats a time. I'm planning this year's seminar titled "rheumatoid hand surgery – Now and Old days" in the meaning that we paid more attention to the new future after having looked back upon the past. At first we discuss about two past presented cases who suffered from "rheumatoid fingers deformities" based on the former discussion and the present conditions. In the light of the discussion, we would like to examine the new case with finger deformities that is presented by rheumatologist. It will be interesting that we discuss whether we take a lesson from the past or not. And as the other topic of "now", I want to take up "ultrasonic examination" that progress impressively and become common in out patients clinic for evaluation of synovitis and inflammation. One case who examined with ultrasonography will be presented by a hand surgeon, and discuss about its availability as the modality for planning the operation. Even the same ultrasonogram, an orthopedist's viewpoint may be different from that of physicians. I would wait for participation of those who are interested in rheumatoid hand reconstruction.

### ES11-1

#### Evidence and daily practice of anti-TNF reagents for RA

Tatsuya Atsumi

Hokkaido University Graduate School of Medicine, Sapporo, Japan

Conflict of interest: Yes

Since 1998, anti-TNF reagents have greatly contributed to improve the outcome of treatment of rheumatoid arthritis. A number of studies have shown that the anti-TNF reagents can inhibit the progression of joint damage as well as providing symptom relief for the affected patients. The term "paradigm shift to the treatment of RA" has been utilised very often in many articles. Since joint damage progression is rarely reversible, early treatment with effective drugs is highly relevant. In this lecture, recent evidence regarding anti-TNF treatment will be reviewed for discussing how to apply those evidence to the daily clinical practice. Certolizumab pegol (CZP) is currently the only PEGylated anti-TNF biologic approved for the treatment of RA. The product is a humanised anti-

gen-binding fragment (Fab') of a monoclonal antibody that has been conjugated to polyethylene glycol. CZP came up as the latest anti-TNF reagent, but we already have two years' experience for its real-world use. The results of some sub-analysis from J-RAPID/HIKARI would be useful to answer some specific questions raised by CZP users. In addition, PRESERVE by etanercept, CONCERTO by adalimumab and some other useful studies will be focused to discuss the topic.

### ES11-2

#### **Is early response, the depth of response, or both to a new therapy in the treatment of rheumatoid arthritis important?**

Roy Fleischmann

University of Texas Southwestern Medical Center, Dallas USA

Conflict of interest: None

The effective treatment of all individuals with rheumatoid arthritis has been an elusive goal for the practicing physician and patient for many years. With the development of multiple new therapies for the treatment of RA over the past 30 years, it has been possible to treat more patients more effectively with a substantial number able to achieve low disease activity or remission. There are now several csDMARDs, a tsDMARD and multiple bDMARDs which can be utilized to reach these goals. We do not, however, have a viable predictor of which patient will respond to which medication or combination of medications and clinically utilizable biomarker to predict response in a given patient to a given medication do not exist at present, although much basic research is in progress to try to help answer this very important question. With the numbers of medications that can be employed, with different mechanisms of action, and understanding that a patient may respond to one medication but not another, it is important to determine early whether a patient will respond to a medication or not. The focus of this discussion shall be what measures or tests can effectively be used to predict long-term response in patients being treated for rheumatoid arthritis and similar inflammatory disease

### ES12-1

#### **Suppression of disease activity of rheumatoid arthritis using sensitive imaging modalities to evaluate synovial inflammation**

Kei Ikeda

Department of Allergy and Clinical Immunology, Chiba University Hospital, Chiba, Japan

Conflict of interest: Yes

The improvement of modern therapeutic strategies in rheumatoid arthritis (RA) has also advanced imaging techniques to evaluate synovial inflammation. The utility of sensitive imaging modalities such as musculoskeletal ultrasound and magnetic resonance imaging (MRI) in the management of RA has been extensively studied as these modalities visualize both synovitis and bone lesions. The direct visualization of synovial inflammation, which is impossible with plain radiograph, caused a paradigm shift in the imaging of RA. Ultrasound and MRI enable more accurate assessment of inflammation in the synovial tissues than does clinical examination. Accurate assessment of synovial inflammation directly improves therapeutic outcome of RA by accurate diagnosis and assessment of disease activity, which enables earlier intervention and tighter control and also reduces unnecessary or inappropriate use of anti-rheumatic drugs. In addition, visualizing synovitis provides rheumatologists with opportunities to better understand the pathophysiology of RA and to improve joint assessment/injection skills and also with a tool to better communicate with patients, which all contribute to improved clinical outcomes. On the other hand, the benefit of advanced imaging modalities should be balanced with its cost and the time spent. In particular, time can be the major obstacle in daily practice. In this presentation, different imaging modalities will be compared and optimal choice of the patients and joints will also be discussed.

### ES12-2

#### **Timing of initiation of TNF inhibiting therapies and control of disease activity in attempts to inhibit the progression of large joint destruction**

Isao Matsushita, Hiraku Motomura, Tomoatsu Kimura

Department of Orthopaedic Surgery, Faculty of Medicine, University of Toyama

Conflict of interest: Yes

In recent years, the treatment of rheumatoid arthritis (RA) have improved drastically, and treatment to achieving remission is expected. Achieving structural remission is particularly important to maintain activities of daily living of patients with RA. Joint damage appears early in the disease course and progresses more rapidly in the earlier phase in RA. Minimizing joint destruction therefore requires early diagnosis, early treatment, and tight control of disease activity using composite measures. However, RA affects various joints, and large weight-bearing joints such as hip and knee joints should not be treated in the same manner as small joints. Inhibiting damage of weight-bearing joints demands effective therapeutic intervention before progression of destruction. On the other hand, surgical intervention should be introduced in RA patients whom large joints have already deteriorated. We previously developed the ARASHI scoring system, which enables more detailed evaluation of large joints than the Larsen grading system in RA. In the evaluation of a total of 182 joints—including 96 hip joints and 86 knee joints—in 51 RA patients treated with TNF inhibitors during 2 years, all joints with a baseline ARASHI score of  $\geq 3$  points showed progression of joint damage within 2 years. In detailed analysis, we found that the joint space narrowing score was strongly correlated with subsequent progression of joint damage than the erosion score. In contrast, only 6.5% of joints with a baseline status score of  $\leq 2$  points showed progression of destruction. Among patients with status score of  $\leq 2$ , patients with progression of joint damage had significantly higher disease activity than those with no progression of damage during TNF inhibiting therapies. In this seminar, I would like to talk about the characteristics of large joint destruction in RA, therapeutic strategies and surgical intervention for preventing joint destruction.

## Annual Course Lecture

### ACL1

#### Management of comorbidities and adverse drug reactions in patients with rheumatoid arthritis

Masayoshi Harigai<sup>1,2</sup>

<sup>1</sup>Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, <sup>2</sup>Department of Rheumatology, Tokyo Medical and Dental University Hospital

Conflict of interest: Yes

Treat-to-target strategy in rheumatoid arthritis (RA) has been proposed and widely accepted as an international consensus, which recommend periodic evaluation of disease activity and intensification of treatment with consideration of benefit-risk balance. Japan College of Rheumatology has announced the guidelines for the management of rheumatoid arthritis in 2014, aiming at standardization of diagnosis and treatment of RA in Japan. In clinical practice, rheumatologists should pay attention to various comorbidities that may develop during the clinical course of RA and to adverse drug reactions (ADRs) of antirheumatic medications. Epidemiological studies revealed that RA is an independent risk factor for death and that top 4 causes of deaths are malignancy, infection, cardiovascular disease and interstitial lung disease in Japan. Among these, increased risk for cardiovascular disease in patients with RA has drawn strong attention and this comorbidity should be properly managed in clinical practice. Management of ADR has been included in various guidelines based on the evidence from clinical trials and cohort studies, placing a special emphasis on early diagnosis and treatment of ADRs. So far, no new safety signal has been detected in the current postmarketing surveillance (PMS) program of methotrexate (MTX) up to 16 mg/week. An additional nation-wide survey for MTX-associated lymphoproliferative disease may be required. All-cases PMS programs for five biologics revealed types of ADRs and their incidence rates. Two major serious ADRs common to biologics were infection and respiratory disorders, especially interstitial lung disease. All-cases PMS program for tofacitinib is currently being implemented. Rheumatologists should manage the increased demand of pretreatment screening of a patient with RA and monitoring of ADRs, especially for infectious diseases, and build their own system for early diagnosis of ADRs in each medical institution.

### ACL2

#### A primer of clinical immunology

Keishi Fujio

Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo

Conflict of interest: Yes

The widespread use of biologics emphasizes the importance of the understanding of immunology. In addition to the previously recognized immune cells including dendritic cells (DCs), T cells and B cells, a new subset associated with natural immunity, innate lymphoid cells (ILCs) have been identified. In T cells, IL-17-producing Th17 cells and IL-21-producing follicular helper T cells joined to the group of well-known IFN-gamma-producing Th1 cells and IL-4-producing Th2 cells. Although CD4+CD25+ regulatory T cells are the major population with regulatory activity, IL-10-producing regulatory B cells are also identified. Besides antibody production, antigen presentation and production of inflammatory cytokine are recognized as important contribution of B cells in chronic inflammation. Among DCs, the role of type I interferon-producing plasmacytoid DCs has been emerged as a key player in autoimmunity. A number of reports describe that these immune cells are the important targets of immunotherapy. Based on these advances, this session is going to show the basic immunological views required for clinical immunology.

### ACL3

#### Pain Management for Rheumatoid Arthritis Patients

Katsunori Ikari

Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: Yes

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease, and controlling the autoimmune response and suppressing the excessive inflammation is the optimal way to control the pain. In recent years, methotrexate and biologic agents have brought about a paradigm shift in the treatment outcome of rheumatoid arthritis, and we entered an era in which it became feasible to make preventing joint destruction, maintaining physical function, etc. However, it is never acceptable to neglect attempting to improve patients' short-term QOL. Discrepancies between global ratings by physicians and patients' global ratings have fairly often been pointed out, but they have also been said to be attributable to physicians' attaching importance to the number of swollen joints when making global evaluations, as opposed to patients' putting greater emphasis on their pain level. Aside from the argument as to whether or not pain is the essence of disease activity evaluations, it should be kept in mind that pain accounts for a high proportion of patients' global evaluations and that physicians may underestimate patients' pain.

### ACL4

#### Psoriatic arthritis: diagnosis and treatment

Atsuo Taniguchi

Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: None

Psoriatic arthritis is one of inflammatory arthritides that is associated with psoriasis. Psoriatic arthritis involves the joints, however it affects the surrounding structures of joints, such as tendon, ligament, and enthesitis. Sometimes inflammation of spine and sacroiliac joint develops, indicating that Psoriatic arthritis is one of spondyloarthritis. Recent investigation showed that psoriatic arthritis had the same disease burden as rheumatoid arthritis and ankylosing spondylitis. Furthermore, it has been reported that early referral to rheumatologists was important to prevent severe joint disease and deterioration of quality of life. Therefore, early prompt diagnosis and treatment are essential to prevent progressive joint damage. The main clinical features of psoriatic arthritis include peripheral arthritis, psoriasis of skin and nails, dactylitis, enthesitis, and axial disease. The recognition of each domain is useful not only for differential diagnosis, but also treatment. It has been estimated that joint involvement is observed in 10% to 30% of patients with psoriasis. The majority of patients develop the skin lesions before the development of psoriatic arthritis. It is desirable for dermatologists and rheumatologists to examine the characteristic features of psoriatic arthritis regularly. Traditional DMARDs have been recommended to treat some of the manifestations of psoriatic arthritis, although the evidence of their effectiveness was not sufficient. However, TNF inhibitors have been demonstrated significant effects on most of the domains. Recently, new drugs that inhibit cytokine have been reported to be effective on psoriatic arthritis. The progress in the treatment of psoriatic arthritis will contribute to the better outcome of the disease.

### ACL5

#### Economic Aspects of Treatment of Rheumatic Disease

Tsukasa Matsubara

Matsubara Mayflower Hospital

Conflict of interest: Yes

Over 10 years have passed since the start of rheumatoid arthritis (RA) treatment with biologics in Japan. They are highly efficacious, and greatly improve symptoms, to the degree that it can rightly be called a paradigm shift. However, they are costly, and as the cost of these drugs continues to rise, it is important to understand the effects on an already financially constricted health care system. Accordingly, an understanding of these factors, and cost-benefit analysis is essential in clinical practice. In addressing these issues, the national health insurance providers and patients have their respective positions and opinions, which differ on some points. Naturally, it is important for clinical practitioners to understand and align with the patient's view. We have calculated and present a cost-per-unit analysis of the cost of reducing disease activity per CDAI. In addition, we analyzed the national financial support available for patients of rheumatic diseases. Disease activity was measured with CDAI and cost effectiveness was calculated per CDAI point reduced. The re-

sults indicated that treatment of patients with high disease activity was more cost-effective than that of patients with medium range disease activity. Careful consideration in choice of medication, the amount utilized, as well as frequency of use, based on disease activity ties into improvement of economic factors. The national disability scale system and sliding pension and income scales can be applied for patients of rheumatic diseases. National Nursing Care insurance can be used by patients of rheumatic diseases from the age of 40. In addition, coverage of a percentage or full coverage of medical fees is possible for patients of juvenile RA, malignant RA, and other collagen diseases. From this it is clear that a full understanding of the economic factors involved in treatment of rheumatic diseases, as well as the support available, is indispensable to the progress and future of RA treatment.

## **ACL6**

### **What we should know about medical law**

Naohiro Watanabe  
Watanabe Law Office

Conflict of interest: None

## **ACL7**

### **The appropriate choice and direction for biologic DMARDs**

Yutaka Kawahito  
Inflammation and Immunology, Kyoto Prefectural University of Medicine, Kyoto, Japan

Conflict of interest: Yes

The primary target for rheumatoid arthritis (RA) treatment should be a state of clinical remission or at least low disease activity for established long-standing disease, was suggested in Treat to Target. At present, we can reach this goal based using biological DMARDs (bDMARDs) which suppress a bone destruction can be used in addition to MTX. How should I choose bDMARDs showing the high effectiveness about 70-80% in daily clinical practice. The guidance for drug choice of bDMARDs is not stated in EULAR, ACR recommendation and JCR 2014 RA treatment guidelines. Important factors of the choice are as follows. First of all, MTX is available or not? Next, whether we can regulate a dose and the interval of administration for patients with many complications to reduce side effects. Furthermore, we should use the drug which can expect prompt effect by regulating the quantity and loading if progression of bone destruction is fast. After adjusting factors noted above, we had better choose one drug depending on situation of daily life and domestic economy. Recently the medical economic matter is considered in RA treatment algorithm in Europe and America. The bone destruction suppressive effect is higher in the bDMARDs than in conventional synthetic DMARDs. The early use of bDMARDs decreases the indirect medical expenses by improving labor productivity, but it also increases the direct medical cost including drug cost. It is said that there are few merits in medical economical matter if we cannot discontinue or cancel bDMARDs. However, cancellation and discontinuation of this drug is difficult at present. So we must maintain the clinical remission reducing the dose of it and use biosimilar reagents. It is important that we think an individual and medical economic cost while considering the immunogenicity such as the antidrug antibody of bDMARDs. In this lecture, I present an outline about the choice of bDMARDs while considering various factors and clinical questions.

## **Annual Course Lecture Luncheon Seminar**

### **ACL-LS**

#### **Efficacy and safety of high-dose methotrexate (MTX) for rheumatoid arthritis (RA)- From the results of special investigation of methotrexate based on post marketing surveillance -**

Yasuo Suzuki

Division of Rheumatology, Department of Internal Medicine, Tokai University School of Medicine

Conflict of interest: Yes

A recent paradigm shift of the treatment of RA is to aim for remission by the T2T strategy, using DMARD as early as possible in the disease process. Among the DMARD, MTX is a highly effective drug both as monotherapy and in combination with other DMARD or biologics. MTX has greater long-term effectiveness, tolerability and safety than any other non-biologic DMARD. Thus, MTX has served as not only a 1st-line drug but also an anchor drug in the treatment of RA. In Japan, an increase in dose of MTX up to 16mg/week was approved in February 23, 2011. At Tokai University Hospital, 84.4% of RA patients receive MTX by monotherapy or combination with biologics (19.8%) or other DMARD (12.8%). The efficacy of MTX increases dose-dependently, although the effects tend to reach a plateau at around 15 mg/week. If MTX is used up to 10 to 12mg/week, higher efficacy and remission rate can be obtained. In addition, higher remission rate was observed when MTX was used as the 1<sup>st</sup> line DMARD compared to the 2<sup>nd</sup> or 3<sup>rd</sup>-line DMARD. The analysis of a post marketing surveillance (PMS) of MTX with higher doses in Japanese RA patients to assess effectiveness and safety has been completed. The results of PMS showed that remission rate increased approximately 3 times by increasing MTX from 8mg to more than 10mg/week in patients with monotherapy as well as patients in combination with biologics. MTX is usually well tolerated in most of RA patients with appropriate folic acid supplementation. However, 541 patients who died during MTX therapy by adverse events have been accumulated until December 31, 2013. As a recent tendency, infection and lymphoproliferative disorders have been increasing probably due to long-term immunosuppression. In this lecture, I discuss the practical points for the use of high-dose MTX and review the latest information regarding efficacy and safety of MTX as an anchor drug including the results of the PMS.

## **AUTHORS' INDEX**

<b>PL</b>	.... <b>Presidential Lecture</b>
<b>RS</b>	.... <b>Representative Session</b>
<b>S</b>	.... <b>Symposium</b>
<b>IS</b>	.... <b>International Symposium</b>
<b>EL</b>	.... <b>Educational Lecture</b>
<b>MTE</b>	.... <b>Meet the Expert</b>
<b>SW</b>	.... <b>Specified Workshop</b>
<b>ICW-C</b>	.... <b>International Concurrent Workshop Clinical</b>
<b>ICW-B</b>	.... <b>International Concurrent Workshop Basic</b>
<b>W</b>	.... <b>Workshop</b>
<b>GES</b>	.... <b>The Subcommittee on Gender Equality Support Program</b>
<b>AP</b>	.... <b>Anaphylaxis Guideline Program</b>
<b>P</b>	.... <b>Poster Session</b>
<b>LS</b>	.... <b>Luncheon Seminar</b>
<b>ES</b>	.... <b>Evening Seminar</b>
<b>ACL</b>	.... <b>Annual Course Lecture</b>
<b>ACL-LS</b>	.... <b>Annual Course Lecture Luncheon Seminar</b>

**Bold Abstract No. .... Presenting Author**

<b>A</b>			
Abe, Akane	P2-240	Akiyama, Yoichiro	W42-2, W59-4, P1-199, <b>P2-236</b> , P3-198
Abe, Asami	W12-1, W15-5, W23-5, <b>W39-1</b> , W45-4, W52-1, W52-3, W71-1, W74-1, GES-3, P3-133	Akiyama, Yuji	ICW-B1-4, W13-4, W60-1, W79-2, P1-173, P1-212, P1-249, P2-026, <b>P2-118</b> , P3-001
Abe, Kyosuke	W70-2, W70-3, W78-5, <b>P1-186</b> , P1-202	Akizuki, Satoshi	P1-029
Abe, Muneki	<b>P2-097</b> , P3-095	Alfredsson, Lars	S17-1
Abe, Saori	W28-3, W49-2, W49-3, W55-3, P1-030, P1-032	Al-Mayouf, Sulaiman M	<b>ICW-C8-5</b>
Abe, Satomi	W19-3, W57-3, P2-051, P3-025, P3-118	Amagai, Masayuki	SW1-2
Abe, Satoshi	S14-3	Amano, Hirofumi	<b>S4-2</b> , W64-1, W64-3, W80-6, P1-163, P1-195, P2-012, P2-013
Abe, Shuji	P3-040, P3-048	Amano, Koichi	<b>S7-3</b> , ICW-C7-3, W16-1, W31-4, W76-3, P1-033, P1-062, P1-115, P3-262
Abe, Takeo	W12-6, <b>W41-6</b> , W43-2, W48-1, W56-3, P1-152, P1-171, P2-166, P2-173, P2-175, P3-116	Amano, Yoshimi	<b>P1-265</b>
Abe, Yoshiyuki	<b>W44-3</b> , W80-6	Amasaki, Yoshiharu	P1-075
Abou Rjeili, Mira	<b>ICW-B5-1</b>	Amato, Anthony A	S17-1
Adachi, Akira	P2-091	Amengual, Olga	ICW-C2-6
Adachi, Masanori	P2-052, P3-047	Amuro, Hideki	W68-5, W82-2, P1-246, P3-186, P3-214
Adams, David	ICW-B2-3	Ando, Kiichiro	<b>P2-124</b>
Aggarwal, Rohit	ICW-C9-5	Ando, Masayasu	P3-105
Aihara, Michiko	P1-151	Ando, Seiichiro	W80-6, <b>P1-162</b> , P2-025, P2-047, P3-043
Aita, Tetsushi	W5-2, W41-3, P1-232, <b>P1-234</b>	Ando, Taiki	P1-187
Aizaki, Yoshimi	ICW-B1-4, W13-4	Anno, Shohei	<b>W81-3</b> , <b>P2-016</b> , P3-014, <b>P3-061</b>
Aizawa, Toshiaki	W75-2, W83-5, P1-085, P1-120, <b>P2-090</b> , P2-094, P2-096, P3-027, <b>P3-082</b>	Antfleck, Daniel	ICW-B5-3
Aizu, Motohiko	W4-2, W44-6, W60-3, P1-209, P1-242, P2-120, P3-192	Antono, Dono	ICW-C1-4
Ajiro, Junya	P3-101	Aochi, Satsuki	W6-1, W19-2, W24-5
Akagi, Masao	P3-100	Aoki, Akiko	<b>P1-207</b> , P3-103
Akahira, Lisa	W40-5, W83-1, P2-042	Aoki, Kazutoshi	<b>P1-033</b> , P1-082, P2-194
Akahoshi, Mitsuteru	W11-1, W17-1, W17-4, W20-4, W47-1, W47-2, W50-6, W64-5, <b>P1-210</b> , P2-202	Aoki, Noriko	W56-4, W57-4, P1-121, P1-247
Akai, Takanori	<b>W19-4</b>	Aoki, Yasuaki	<b>P1-238</b>
Akai, Yasuhiro	ICW-C1-5, W46-5, P1-106, P1-194, P2-193, P2-268, P3-218, P3-227	Aoki, Yuko	P1-031, P2-085, P3-260
Akaike, Harumi	W26-2, <b>W26-3</b> , W26-6	Aonuma, Hiroshi	W75-2, W83-5, P1-085, P1-120, P2-090, P2-094, <b>P2-096</b> , P3-027, P3-082
Akamine, Masaki	<b>P3-255</b>	Aoyagi, Kiyoshi	S10-1, ICW-C1-2, W33-1, P1-061, P2-045
Akashi, Kengo	W13-6, W17-5, W34-1, <b>P3-068</b> , P3-208	Arai, Hidenori	W59-3
Akashi, Koichi	W11-1, W17-1, W17-4, W20-4, W47-1, W47-2, W50-6, W64-5, P1-210, P2-202	Arai, Katsumitsu	ICW-B7-6, W2-6, P1-133, <b>P3-101</b> , P3-142
Akashi, Yoshihiro	P2-032	Arai, Sadachika	<b>P3-253</b>
Akebo, Hiroyuki	<b>P3-156</b>	Arai, Satoko	W55-5, P1-083, P3-109, P3-113, P3-266
Akiba, Haruhiko	W13-4, W60-1, P1-173, P1-212, P1-249, P2-118	Araki, Hiroki	<b>W5-4</b>
Akimoto, Masaki	<b>W56-4</b> , W57-4, P1-121, P2-158	Araki, Manabu	IS2-5
Akioka, Shinji	P2-188, P2-224, P3-126	Araki, Yasuto	ICW-B1-4, <b>W13-4</b> , W60-1, P1-212, P1-249, P2-118
Akita, Kanae	ICW-B8-2, W65-5, <b>P1-243</b>	Araki, Yoshihiro	P2-092
Akita, Shosuke	<b>S12-3</b> , W45-5, W54-2, P1-130	Aramaki, Toshiyuki	W20-1, W22-6, W64-6, P1-063, P1-269, P2-048, P2-178, <b>P3-006</b>
Akiya, Kumiko	W28-5, W76-4, W76-5, P2-140, <b>P3-206</b> , P3-210	Ariane, Anna	<b>ICW-C1-4</b>
Akiyama, Mitsuhiro	<b>ICW-C4-2</b> , <b>ICW-B5-7</b>	Arii, Kaoru	<b>W6-3</b> , W67-6
		Arima, Kazuhiko	W22-6, W62-4, P1-061, P1-160, P2-045, P2-048
		Arima, Naomichi	P2-158
		Arima, Takayasu	W75-6

Arimitsu, Sayuri	P3-044, P3-045, P3-054	W56-3, P1-152, P1-171, P2-166,
Arimura, Yoshihiro	S15-1, W25-3, W25-4, W44-5,	P2-173, P2-175, P3-116, <b>P3-204</b>
Arinobu, Yojiro	W7-1, W11-1, W17-1, W17-4,	P2-052, P3-047
	<b>W20-4</b> , W47-1, W47-2, W50-6,	W24-4, P1-172, P2-154, P2-206,
	W62-5, W64-5, P1-210, P2-202	P2-207, P2-209, P3-062, P3-071,
Arinuma, Yoshiyuki	W22-2, W48-3, <b>W65-2</b> , W78-1,	P3-156, P3-168
	W80-1, P1-157, P2-074, P2-101	
Arishima, Yoshiya	W57-4, P1-121, P1-247	
Arita, Yoshiyuki	W62-5, P1-027	
Aritaki, Ai	P2-268	
Arito, Mitsumi	P1-010, <b>P1-011</b> , <b>P1-012</b> , P1-198,	
	P2-163	
Asada, Hideo	<b>S14-2</b>	
Asada, Maki	<b>W7-6</b> , W19-4, W72-4, P3-016	
Asada, Naohiro	<b>P1-090</b> , <b>P1-091</b> , <b>P1-144</b>	
Asahina, Ichizo	P1-134	
Asai, Nobuyuki	ICW-C1-3, W1-4, <b>W2-3</b> , W11-6,	
	W12-3, W12-4, W12-5, W19-5,	
	W23-3, W36-1, W39-6, P1-043,	
	P1-067, <b>P1-097</b> , P1-138, P2-125,	
	P3-012	
Asai, Osamu	<b>P3-079</b>	
Asai, Shuji	ICW-C1-3, W12-3, W12-4, W12-5,	
	W19-5, W23-3, W36-1, W38-5,	
	<b>W39-6</b> , W57-1, P1-043, P1-067,	
	P1-097, P1-114, P1-138, <b>P2-125</b> ,	
	P3-012	
Asako, Kurumi	SW1-3, W6-2, W68-4, P1-018,	
	P2-213, P2-218, <b>P2-221</b> , P2-227	
Asami, Yukiko	W32-5	
Asano, Tomoyuki	P2-185, P2-211, <b>P3-030</b> , P3-184	
Asano, Yosuke	ICW-C8-3, W4-5, <b>W48-4</b>	
Asano, Yusuke	W72-2, P3-057	
Asashima, Hiromitsu	S6-6, <b>ICW-B4-5</b> , ICW-B5-4, W28-3,	
	W49-2, W49-3, W55-3, W62-1,	
	P1-032, P2-011	
Asato, Kayo	W21-2, W30-1, W59-5, P1-240,	
	P2-031, P2-142, P3-152	
Ashihara, Konomi	<b>W44-2</b> , P1-178, P3-080, P3-183	
Asonuma, Kazuyo	P2-267	
Atkins, Gerald J.	ICW-C6-3	
Atsumi, Tatsuya	<b>SW2-8</b> , ICW-C2-6, ICW-B4-7, <b>W1-1</b> ,	
	W1-2, W1-3, W1-5, W11-4, W25-2,	
	W69-2, W69-3, <b>ES11-1</b>	
Atsumi, Toru	<b>W20-2</b>	
Auernheimer, Vera	ICW-B2-3	
Ayabe, Keio	P1-268, <b>P3-102</b>	
Ayabe, Takehiko	P3-040, P3-048	
Ayano, Masahiro	W17-1, W17-4, W20-4, W50-6,	
	W64-5, P1-210	
Azukizawa, Masayuki	<b>W39-4</b> , W71-3, W71-5, W72-3,	
	P3-036	
Azuma, Chinatsu	<b>P3-231</b>	
Azuma, Kota	W43-2, W56-3, <b>P2-173</b> , P2-175,	
	P3-116	
Azuma, Masahiko	P3-141	
Azuma, Naoto	<b>S6-4</b> , W12-6, W41-6, W43-2, W48-1,	
Azuma, Takanori		
Azuma, Teruhisa		
<b>B</b>		
Baba, Hiroyuki	P2-229, P3-003, P3-220	
Baba, Sayumi	P1-219	
Baba, Yuta	<b>P2-219</b>	
Bain, Gretchen	ICW-B2-5	
Bando, Yuki	W22-5	
Bang, Jihye	ICW-B4-3, ICW-B4-4	
Bannai, Ei	W40-5	
Banno, Shogo	<b>W66-5</b> , <b>LS1</b> , P2-039	
Barohn, Richard J	S17-1	
Baron, Roland	<b>IS1-1</b>	
Benson, Merrill D.	W61-4	
Beppu, Moroe	P1-003, P1-011, P1-012	
Bertoncelj, Mojca Frank	ICW-B6-3	
Bessho, Masahiko	W75-5	
Blati, Meryem	ICW-B5-1	
Bogduk, Nikolai	ICW-C6-2	
Bohgaki, Miyuki	W8-5, W56-6	
Bohgaki, Toshiyuki	ICW-C2-6, W11-4	
Bottai, Matteo	S17-1	
Bubb, Michael R.	P2-021	
<b>C</b>		
Cai, Zhe	<b>ICW-B8-5</b>	
Cai, Zhihong	W69-4	
Calise, S. John	P2-021	
Castelino, Flavia V	<b>ICW-B2-5</b>	
Chan, Edward K.L.	P2-021	
Chen, Ta-Liang	ICW-C7-1	
Chen, Weijia	<b>P2-035</b> , P2-132	
Chen, Zhen	<b>ICW-B8-6</b>	
Chiba, Asako	P1-015, P1-016, P1-017	
Chiba, Junji	W72-5	
Chiba, Koki	W75-6	
Chiba, Noriyuki	W29-4, W29-6, W64-1	
Chifu, Yutaka	P2-168	
Chikugo, Momoko	<b>P2-255</b>	
Chin, Hou	W49-4, P2-066	
Chinen, Naofumi	<b>W16-3</b> , W51-4, P1-139, P1-181,	
	<b>P2-069</b> , P2-176, P3-233	
Chino, Kentaro	ICW-C7-3, W16-1, W76-3, P1-033,	
	P1-062, P1-115, <b>P3-262</b>	
Chino, Kozo	P2-049	
Cho, Soo-Kyung	ICW-C6-1	
Choi, Yun Young	ICW-C6-1	
Chosa, Etsuo	W83-2, W83-4, P3-021	
Chu, Man	<b>ICW-B9-4</b>	
Cohen Tervaert, Jan Willem	<b>S15-3</b> , <b>LS29</b>	
Collinge, Mark	W15-1, W15-3	
Craft, Joseph	<b>S13-5</b>	



<b>D</b>			
Daigaku, Aiko	W25-5	Fujibayashi, Takayoshi	W1-4, W2-2, W2-3, W12-3, W23-3, W36-2, W36-4, W38-5, P1-050, P1-100, P1-114, <b>P2-119</b>
Date, Hideki	S3-2, P2-134		
Date, Ryo	<b>P1-143</b>	Fujii, Hiroshi	<b>ICW-B8-2</b> , W4-2, W44-6, <b>W60-3</b> , W62-6, W65-5, W67-4, P1-209, P1-242, P1-243, P2-120, P3-192
Davey, Rod	ICW-B5-3		
Defranoux, Nadine	ICW-C1-6, P3-015	Fujii, Kenji	<b>P1-095</b>
Deguchi, Hitoshi	P3-099	Fujii, Kentaro	P1-193
de Visser, Marianne	S17-1	Fujii, Ryoji	P1-003
Dobashi, Hiroaki	W9-4, W28-4, W33-6, W34-3, W61-6, W65-6, LS13, P1-009, P1-237, P3-222	Fujii, Takao	W30-5, W31-6, W32-4, W39-4, W50-1, W56-2, W59-3, W63-5, W63-6, W65-1, W71-3, W71-5, W82-3, <b>ES4-1</b> , P1-140, P3-036
Doi, Kosuke	<b>P2-206</b>		
Doi, Takumi	P3-261	Fujii, Toshiyuki	<b>P2-081</b>
Dong, Xu	<b>ICW-C9-1</b>	Fujii, Wataru	ICW-C3-4, ICW-B1-6, <b>ICW-B7-5</b> , W24-2, W27-5, W40-1, P1-236, P3-067, P3-153, P3-185
Dörner, Thomas	<b>LS26-2</b>		
Duan, Hongxia	ICW-B9-5	Fujii, Yosuke	P2-137
Duong, Le T.	<b>IS1-5</b>	Fujii, Yuko	P2-230
<b>E</b>		Fujikawa, Keita	W7-1, W9-6, W22-6, <b>P3-026</b>
Ebato, Takasuke	W22-5	Fujikawa, Satoshi	P3-220
Ebe, Hiroshi	S6-6, ICW-B1-2, ICW-B3-3, ICW-B7-1, W13-2, W28-3, <b>W49-2</b> , W49-3, W55-3, P1-001, P1-030, P1-032	Fujikawa, Yoshikazu	P1-170, <b>P1-231</b> , P3-155
Ebina, Kosuke	<b>ICW-C6-6</b> , <b>ICW-C6-7</b> , ICW-B4-2, W57-5, P1-130, P2-079, P3-045	Fujiki, Youhei	W24-3, <b>P2-152</b> , P3-190, P3-212
Eguchi, Katsumi	ICW-C1-2, W1-1, W1-2, W1-3, W1-5, W1-6, W9-6, W22-3, W22-6, P2-045, P3-224, P3-259	Fujimoto, Ayako	W67-2, P1-153, <b>P1-189</b> , P1-205, P2-141
Eguchi, Kouhei	W18-5, P2-184, P2-232		
Eiraku, Nobutaka	W7-1, W56-4	Fujimoto, Jun	P2-057, P2-061, <b>P2-244</b>
Emery, Paul	<b>IS3-3</b>	Fujimoto, Manabu	<b>S17-3</b>
Emoto, Kahaku	W69-4	Fujimoto, Takashi	ICW-C1-5, W56-2, P1-106, P2-268
Endo, Akiko	W25-3, W25-4, P3-197	Fujimura, Kenjiro	P1-142, P3-134
Endo, Hirahito	<b>S4-4</b> , P3-002	Fujimura, Takanori	<b>ICW-C1-5</b> , <b>P1-106</b> , P2-268
Endo, Koji	P2-220	Fujinaga, Hiroshi	W36-3, <b>P2-064</b>
Endo, Naoto	ICW-C6-4, ICW-B7-6, W2-6, W57-6, P1-038, P1-045, P1-133, P2-083, P3-127, P3-142	Fujio, Keishi	S11-4, <b>S16-4</b> , ICW-C5-6, ICW-B3-4, ICW-B3-6, ICW-B7-3, ICW-B7-4, ICW-B8-3, ICW-B9-3, W17-2, W22-4, W28-1, W66-1, W79-6, W80-5, W83-1, <b>ACL2</b> , <b>LS10-1</b> , P1-260, P2-042
Endo, Ryuta	P1-220		
Endo, Wataru	P1-012	Fujio, Natsuki	W28-6, W42-1, <b>W59-2</b> , W76-6, P1-104, P1-146, P2-033, P2-034
Endo, Yukari	<b>P1-187</b>		
Endo, Yushiro	<b>P1-218</b>	Fujioka, Kazuki	ICW-C3-4, <b>ICW-B1-6</b> , ICW-B7-5, W24-2, W40-1, P1-236, P3-067, P3-153
Engler, Adam	ICW-B2-3		
Enomoto, Hiroshi	P1-148	Fujioka, Kei	<b>W68-6</b> , P1-191, P3-243
Eri, Toshiki	<b>W40-5</b> , W83-1, P2-042	Fujisawa, Junichi	ICW-C6-4, ICW-B7-6, <b>W2-6</b> , W57-6, <b>P1-038</b> , P1-045, <b>P1-133</b> , P2-083, P3-127, P3-142
Esaki, Yukio	W40-6, <b>P1-142</b> , P3-128, P3-131, P3-134, P3-140		
Eshiro, Hisako	P2-097, <b>P3-095</b>	Fujisawa, Taro	W4-3, <b>P2-167</b>
Etani, Yuki	<b>P1-135</b> , P2-122	Fujisawa, Yuhei	W60-3
Eto, Hikaru	SW1-5	Fujisawa, Yuki	ICW-C2-3, ICW-C2-4, ICW-C7-2, P3-004
Ezawa, Kazuhiko	W11-3, W45-1, W56-5, W73-3, P3-117		
Ezawa, Naoki	P2-155, P2-200	Fujisaza, Yuki	ICW-C5-4
<b>F</b>		Fujishiro, Daisuke	W18-5, P2-184, <b>P2-232</b>
Findlay, David M.	ICW-C6-3	Fujishiro, Maki	W17-6
Fleischmann, Roy	<b>ES11-2</b>	Fujita, Hiroyuki	ICW-C9-6
		Fujita, Kazuyuki	W43-1, P1-211, <b>P2-112</b>
		Fujita, Kumi	W24-4
		Fujita, Mamoru	P3-130
		Fujita, Masaaki	ICW-C5-3, P2-157



Goulet, Lance	ICW-B2-5		P2-217, P3-107
Greth, Warren	W69-5	Hanaoka, Ryosuke	P2-062, <b>P3-060</b>
Guo, Xiaoxiao	ICW-C7-6	Hanata, Norio	ICW-B3-4, ICW-B7-4, ICW-B9-3, W22-4, W28-1
<b>H</b>		Handa, Yuichi	W6-3, W67-6, P3-160
Hada, Shinnosuke	S3-1	Haneda, Masakazu	W18-5, W74-1, P2-184, P2-232
Haga, Nobuhiko	<b>EL7</b> , W63-2, W83-6	Hanibuchi, Masaki	P2-257
Haga, Shiori	P2-020	Hanyu, Tadamasu	W6-3, W52-5, W67-6
Hagihara, Keisuke	ICW-C6-6, <b>W46-2</b> , <b>W57-2</b> , P3-234	Hara, Akinori	P1-203, P2-156
Hagino, Hiroshi	<b>S2-2</b> , P2-053, P2-054	Hara, Ryoki	W69-3
Hagino, Noboru	P2-183	Hara, Ryota	<b>S12-5</b> , ICW-C1-5, P1-106, P2-268
Hagiwara, Kiyofumi	P1-224, <b>P1-263</b>	Hara, Satoshi	W4-2, W44-6, W60-3, <b>P1-209</b> , P1-242, P2-120, P3-192
Hagiwara, Shigeo	P2-136	Hara, Yuki	<b>P3-238</b>
Hagiwara, Shinya	S6-6, W28-3, W49-2, W49-3, <b>W55-3</b> , P1-030, P1-032	Harada, Hiroaki	W22-4, W66-1, W83-1, P2-042
Hagiwara, Takafumi	<b>W56-1</b>	Harada, Hiroshi	<b>P2-087</b>
Hagiya, Chihiro	P1-032	Harada, Koji	<b>W46-5</b> , P1-194, P2-193, P3-218, P3-227
Hagiyama, Hiroyuki	W6-3, W67-6, P2-248	Harada, Ryoza	<b>W39-5</b> , W71-2, P1-129, P1-264, P2-270
Haji, Yoichiro	<b>P3-265</b>	Harada, Tomoya	ICW-B3-5, <b>W5-5</b> , W77-5, P2-150
Hajiro, Takashi	<b>MTE18</b>	Harada, Yoshinori	ICW-C4-6, W16-5, W31-2, W32-1, W54-2, P1-127, P2-024, P2-241
Hakamata, Minako	P1-245, <b>P3-228</b>	Haraguchi, Kazushi	<b>P1-262</b> , <b>P3-147</b>
Hakamata, Yasuhiro	P1-222	Haranaka, Miwa	<b>P2-162</b>
Haku, Takashi	P2-240	Haraoka, Hitomi	<b>ICW-C4-4</b> , ICW-C9-4, W12-2, W34-6, GES-3, P2-171, P2-203, P3-024
Hama, Maasa	ICW-C2-1, ICW-C2-2, W7-2, W8-3, W21-4, W32-5, W79-3, <b>W80-2</b> , P2-235	Harigae, Hideo	S1-5, ICW-B8-2, W65-5, P1-243
Hamada, Daisuke	<b>P1-004</b>	Harigai, Masayoshi	S15-1, <b>SW2-5</b> , SW2-6, W23-1, <b>W29-2</b> , W31-4, <b>ACL1</b> , <b>LS16</b>
Hamada, Hiroaki	W7-1, W83-2, W83-4, <b>P3-021</b>	Harigai, Takako	P3-105
Hamada, Kazuya	<b>P3-215</b>	Harigane, Kengo	W12-1, W15-5, W23-5, W45-4, W52-1, <b>W52-3</b> , W71-1, W74-1, P1-110, P2-133
Hamada, Masanori	P3-143	Hariu, Mitsuhiro	<b>W53-2</b> , P1-134
Hamada, Takuya	P1-252, P3-005	Haro, Hirotaka	W20-3, W39-3, P2-049
Hamada, Yuto	W38-4, W70-6, W74-2, P2-060, P3-075, <b>P3-092</b> , P3-093, P3-236	Hasebe, Narumi	S15-1
Hamaguchi, Marina	<b>P2-203</b>	Hasegawa, Eiko	W2-5, W4-6, <b>W21-6</b> , W48-5, W78-6, P2-107
Hamaguchi, Masahide	W59-3, W82-3	Hasegawa, Hisanori	<b>S17-6</b>
Hamamoto, Kae	W60-2, <b>P1-251</b>	Hasegawa, Hitoshi	W51-6, P2-252, P3-180
Hamamoto, Yosuke	W39-4, W71-3, W71-5, W72-3, <b>P3-036</b>	Hasegawa, Ken	W7-5, <b>P1-117</b>
Hamano, Ryoko	P1-242, P3-192	Hasegawa, Masahiro	P3-069
Hamano, Yoshimasa	W20-5	Hasegawa, Naoki	<b>MTE13</b>
Hamasaki, Hajime	P2-162	Hasegawa, Taishi	P3-088
Hamasato, Kazuhiro	<b>P1-220</b>	Hasegawa, Takakazu	P2-179, <b>P2-197</b> , P3-188
Hamatani, Hiroko	W5-4	Hasegawa, Takashi	<b>W10-2</b> , W10-5, W53-3, W53-4, P2-130
Hanabayashi, Masahiro	W1-4, W36-2, <b>W36-4</b> , W38-1, W38-5, P1-114	Hasegawa, Yasuyuki	<b>ICW-B3-5</b> , P2-190
Hanafusa, Toshiaki	W24-3, W27-1, W27-4, W80-3, P1-165, P1-245, P2-027, P2-123, P2-152, P2-172, P2-189, P2-245, P3-051, P3-120, P3-190, P3-212, P3-228, P3-240	Hashiba, Yayoi	W54-5, P1-078, P1-156
Hanai, Akiko	W59-3, W82-3	Hashimoto, Atsushi	<b>W29-4</b> , P1-183, P1-241, P2-059, P2-247, <b>P3-018</b> , P3-112, P3-247
Hanai, Shunichiro	<b>P3-198</b>	Hashimoto, Hideo	W56-2
Hanami, Kentaro	ICW-C1-6, ICW-B6-2, <b>W41-2</b> , <b>P3-015</b>	Hashimoto, Hiroo	<b>P3-230</b>
Hanaoka, Hironari	ICW-B3-1, W59-1	Hashimoto, Hiroshi	S15-1, W64-1
Hanaoka, Masanori	W5-5, W48-2, W64-2, W65-3, W77-5, P1-154, P1-155, P1-167, P1-219, <b>P1-244</b> , P2-150, P2-198,	Hashimoto, Jun	<b>S2-1</b> , S12-3, ICW-C4-6, ICW-C6-6, ICW-C6-7, W16-5, W31-2, W32-1,

	W45-5, W54-2, W63-2, W83-6, P1-127, P1-130, P2-024	Henmi, Mihoko	P1-031, P2-085, P3-260
Hashimoto, Keisuke	P2-052, P3-047	Hidaka, Misaki	S15-1
Hashimoto, Motomu	W30-5, W31-6, W32-4, W39-4, W56-2, W59-3, W63-5, W63-6, W65-1, W71-3, W71-5, W82-3, P1-140, P3-036	Hidaka, Toshihiko	ICW-C1-2, W7-1, <b>W54-5</b> , W56-2, P1-072, <b>P1-078</b> , P2-121, P3-090
Hashimoto, Naoaki	W12-6, <b>P3-205</b>	Higami, Kenshi	W56-2
Hashimoto, Naonori	P1-007, <b>P1-059</b>	Higashi, Kayoko	P3-042, P3-052
Hashimoto, Sanshiro	P3-065	Higashioka, Kazuhiko	W73-4, P2-098, P2-115, <b>P2-147</b> , P3-035, P3-239
Hashimoto, Shuko	W24-4, P1-172, <b>P2-154</b> , P2-206, P2-207, P3-062, P3-071, P3-156, P3-168	Higuchi, Makiko	W3-2, W50-3, W77-6, P2-111, <b>P2-216</b> , P3-070, P3-173, P3-176, P3-178
Hashimoto, Takenori	P3-205	Higuchi, Tomoaki	<b>W77-1</b> , W77-3, W77-5, P1-167
Hashimoto, Teppei	W18-2, P1-007, P1-059	Higuchi, Toshie	W77-4, <b>P3-033</b> , <b>P3-179</b>
Hashimoto, Yoshiko	<b>P3-091</b>	Higuchi, Yoshihiro	W62-5, <b>P1-027</b>
Hashiramoto, Akira	W18-2, P1-007, P1-040, P1-059	Hino, Shoichi	W21-2, W30-1, W59-5, P1-240, P2-031, P2-142, P3-152
Hashizume, Kenzo	S10-3, W39-5, <b>W71-2</b> , P1-129, P1-264, P2-270	Hino, Takuya	W12-6, W41-6, W43-2, W48-1, W56-3, P1-152, P1-171, P2-166, P2-173, <b>P2-175</b> , P3-116
Hashizume, Misato	ICW-C4-3, P1-024, P2-010	Hinoshita, Tetsuya	MTE8
Hasunuma, Tomoko	W28-6, W42-1, W59-2, W76-6, P1-104, P1-146, P2-033, P2-034	Hirabara, Shinya	W1-4, W16-2, W16-4, W16-6, W32-2, W36-4, <b>W38-5</b> , W57-1, W76-2, P1-047, P1-099, <b>P1-114</b> , P1-116, <b>P3-020</b>
Hata, Kenichiro	W4-1, W27-1, <b>P2-018</b> , P3-194	Hirabayashi, Yasuhiko	<b>W11-5</b> , P3-040, P3-048
Hatachi, Saori	ICW-C5-3, P2-157, P2-186	Hiraga, Masao	<b>W7-3</b>
Hatano, Hiroaki	W22-1, W50-2	Hiraguri, Masaki	W43-5, P3-223
Hatano, Masaru	W28-1	Hirahara, Shinya	<b>W68-3</b> , P3-085
Hatano, Ryo	<b>W79-5</b>	Hirai, Kenichiro	W6-5, P2-113
Hatta, Kazuhiro	W24-4, <b>P1-172</b> , P2-154, P2-206, P2-207, <b>P2-209</b> , <b>P3-062</b> , P3-071, P3-156, P3-168	Hirai, Takuya	W81-6, <b>P1-233</b> , P2-149, P3-161, P3-201, P3-226
Hattori, Toshiyuki	W11-4	Hirai, Yasuko	ICW-C8-1, W34-4, W37-6, W41-5, W64-6, <b>P1-148</b> , P1-160, P2-045, P2-205, P3-094, P3-238
Hattori, Yosuke	W1-4, <b>W2-2</b> , W29-1, W42-6, W73-6, W74-4, <b>ES6-1</b> , <b>P1-050</b> , P1-069, <b>P1-100</b> , P1-114, P2-145	Hirai, Yoshihiro	P1-245, P3-228
Hayakawa, Kazue	S3-2, <b>P2-134</b>	Hirakata, Michito	<b>MTE17</b>
Hayakawa, Kunishiro	W17-6	Hiramatsu, Katsutoshi	W23-1
Hayakawa, Masakatsu	ICW-C3-2, W38-3	Hiramatsu, Rikako	W2-5, W4-6, W21-6, W48-5, W78-6, P2-107
Hayakawa, Satoshi	W25-3, W25-4, W80-4, P1-058, P3-046	Hiramatsu, Sumie	<b>W32-4</b>
Hayami, Noriko	W4-6, W21-6, <b>W48-5</b> , W78-6, P2-107	Hiramatsu, Yuri	<b>P1-165</b> , P2-027
Hayami, Yoshihito	<b>P2-253</b>	Hirano, Daisuke	W44-2, <b>P1-178</b> , P3-080, P3-183
Hayashi, Eri	W34-2, P1-015, <b>P1-016</b> , P1-017	Hirano, Fuminori	<b>P2-144</b>
Hayashi, Haeru	W46-4, P2-008	Hirano, Fumio	W29-2, <b>W31-4</b>
Hayashi, Hiroki	<b>P2-240</b>	Hirano, Hiroyasu	<b>P1-026</b>
Hayashi, Junji	P1-033, <b>P1-055</b>	Hirano, Norikazu	<b>P3-037</b>
Hayashi, Masatoshi	W1-4, W11-6, W12-3, W23-3, W36-1, W36-2, W36-4, W38-5, P1-099, P1-114, <b>P2-004</b>	Hirano, Toru	ICW-B4-2, IS2-2, W11-2, W20-5, P1-193, P1-255
Hayashi, Norihide	ICW-C2-3, <b>ICW-C2-4</b> , ICW-C7-2	Hirano, Yuji	W1-4, W2-2, W2-3, W11-6, W12-3, W12-5, <b>W16-2</b> , W16-4, <b>W16-6</b> , W23-3, W32-2, W36-1, W36-2, W36-4, W38-5, <b>W57-1</b> , <b>W76-2</b> , <b>P1-047</b> , P1-050, P1-067, P1-069, <b>P1-099</b> , P1-100, P1-114, <b>P1-116</b> , P2-119, P3-020
Hayashi, Noriyuki	<b>S18-4</b> , <b>W60-2</b>	Hirao, Makoto	ICW-C6-6, ICW-C6-7, W16-5, W57-5, <b>P1-130</b> , P3-045
Hayashi, Ryuji	W48-6	Hirase, Nobuhisa	<b>P3-172</b>
Hayashi, Satoko	<b>W73-1</b>		
Hayashi, Shinya	P1-040, P1-044, P1-046		
Hayashibara, Masako	P2-053, P2-054		
Hayashida, Jun-Nosuke	S6-1		
Hazue, Ryo	W78-6, P2-107		
Heike, Toshio	EL6		
Hemmi, Seiichiro	W25-6, P1-197		

Hirata, Akie	P2-001, <b>P2-002</b>	Horikoshi, Masanobu	P1-206, P1-223, P2-246
Hirata, Ayako	<b>ICW-C2-3</b> , ICW-C2-4, ICW-C5-4, ICW-C7-2, P3-004	Horino, Taro	W33-2, <b>P1-169</b> , P1-196, <b>P2-196</b> , P3-199, P3-213
Hirata, Goh	W40-6, P1-142, P3-128, P3-131, P3-134, P3-140	Horita, Masahiro	S10-3, W39-5, W71-2, <b>P1-129</b> , P1-264, P2-270
Hirata, Shintaro	S6-6, <b>ICW-C1-6</b> , ICW-C3-5, ICW-C9-3, <b>ICW-B6-2</b> , W41-2, W49-6, W55-1, W70-4, W77-2, P1-086, P3-015	Horita, Shigeto	W4-2, W44-6, W60-3, P1-209, <b>P1-242</b> , P2-120, P3-192
Hirata, Shinya	<b>W67-2</b> , P1-153, P1-189, P1-205, P2-141	Horita, Tetsuya	ICW-C2-6, W11-4
Hirayama, Tomoyuki	ICW-C1-1, W53-6, P1-141, P3-089	Horiuchi, Hisayo	<b>ICW-C5-2</b> , W3-5, W8-2, W15-6, P1-176, P1-265, P2-226
Hirohata, Shunsei	<b>S8-3</b> , W22-2, W48-3, W64-1, W65-2, W68-2, W68-4, W78-1, W80-1, P1-157, P2-037, P2-074, P2-101, P2-218, P2-221	Horiuchi, Takahiko	W11-1, W21-3, W62-5, P1-027
Hiromasa, Tsutomu	W79-4, P1-158	Horizonzo, Hidehiro	P3-231
Hiromura, Keiju	W5-4, W29-3, W69-2, W69-3, W79-2	Hosaka, Kunihiko	ICW-C6-3, P2-130
Hirosaki, Yuri	<b>W17-1</b> , W17-4, W20-4, W50-6, W64-5, P1-210	Hosen, Naoki	P1-255
Hirose, Jun	<b>W63-3</b>	Hoshi, Daisuke	W31-1, W31-3, W31-5, W66-6, W67-5, W77-5, P1-154, P2-005, P2-150, P2-198, P2-217, <b>P3-050</b> , P3-107
Hirose, Koichi	W24-6, W50-4	Hoshi, Kenichi	P2-155, P2-200
Hirose, Sachiko	W64-3, P2-012, P2-013	Hoshida, Yoshihiko	P1-127
Hirose, Tatsuo	<b>P2-070</b>	Hoshino, Junichi	W2-5, W4-6, W21-6, W48-5, W78-6, P2-107
Hirose, Tomohiro	W15-1, W15-2, W15-3, W15-4	Hoshino, Keisuke	P2-084, P3-136
Hirose, Wataru	<b>P1-066</b>	Hoshino, Koyu	W67-2, P1-153, P1-189, P1-205, <b>P2-141</b>
Hiroshima, Ryo	W19-6, P2-129, P3-055	Hoshioka, Akira	P3-209
Hirota, Takuo	W4-3, P2-167	Hoshiyama, Takayuki	W80-1, <b>P2-101</b>
Hirota, Tomoya	S6-6, ICW-B4-5, ICW-B5-4, W28-3, W49-2, W49-3, W55-3, W62-1, <b>P1-030</b> , P1-032, <b>P2-011</b>	Hosono, Osamu	W18-6
Hisa, Kaori	<b>W9-3</b>	Hosono, Yuji	W41-6, W48-1, <b>W50-1</b> , W51-3
Hisada, Ryo	W11-4	Hosoya, Tatsuo	ICW-B2-6
Hisamoto, Satomi	W17-1, W17-4, W20-4, W50-6, W64-5, P1-210	Hosozawa, Tetsuji	W72-1, <b>P3-053</b>
Hisano, Mayu	P1-266	Hsieh, Song-Chou	ICW-C7-5
Hisazawa, Kaori	<b>P1-266</b>	Huang, Can	ICW-C7-6
Hishinuma, Ruka	P1-123	Huang, Shir-Ly	<b>ICW-B8-4</b>
Hishitani, Yoshihiro	W11-2, <b>P3-099</b>	Huizinga, Tom W	<b>S13-4, ES3-2</b>
Honda, Kiri	W16-3, W51-4, P1-112, P1-181, P2-176, P3-158, P3-175		
Honda, Seiyo	ICW-C1-2	<b>I</b> —————	
Honda, Zen-ichiro	SW1-3, W6-2	Iba, Hiroki	P2-263
Hongo, Michio	W75-2	Ichida, Hisae	W48-2, W64-2, W65-3, W77-3, W77-5, P1-154, P1-155, P1-167, <b>P1-219</b> , P1-244, P2-150, P2-198, P2-217, P3-107
Honjo, Shigeru	W82-6, P1-060, P2-116	Ichida, Kimiyoshi	ICW-B2-6
Honne, Kyoko	W59-4	Ichihara, Shie	P2-039
Honoki, Hiroyuki	W48-6, <b>P2-195</b> , P2-204, P3-150, P3-159, P3-193	Ichikawa, Kazunobu	P1-141, P1-159
Horai, Yoshiro	S6-3, S6-6, ICW-C8-1, W33-1, W34-4, W37-6, W41-5, W62-4, W64-6, P1-061, P1-160, P2-045, P2-048, P2-205, P3-094, P3-238	Ichikawa, Naomi	S5-2, W19-1, <b>P1-261</b> , P2-259
Horaiya, Koji	MTE8	Ichikawa, Takanori	<b>P2-155</b>
Horie, Koichiro	P1-183, P1-241, P2-247, P3-018, P3-112, P3-247	Ichimura, Yuki	<b>W77-5</b>
Horikawa, Yukio	W4-3, P2-167	Ichinose, Kunihiko	ICW-C8-1, W20-1, W33-1, W34-4, W37-6, W41-5, W64-6, P1-061, <b>P1-160</b> , P2-045, P2-048, P2-205, P3-006, P3-094, P3-238
Horikoshi, Hideyuki	W6-1, <b>W19-2</b> , W24-5	Ichise, Yoshihide	W41-4, W70-2, W70-3, <b>W78-5</b> , P1-186, P1-202
Horikoshi, Keisuke	<b>P1-203</b>	Ida, Hiroaki	ICW-B3-2, W7-1, <b>W9-2</b> , P1-175, P2-231
		Ideguchi, Haruko	W32-5, P2-159, <b>P3-081</b>
		Ideura, Hiroshi	P3-114

Ido, Akiko	W66-3, P1-161, P2-110, P3-187	Imuro, Takashi	<b>P2-223</b>
Ido, Akio	<b>MTE20</b>	Inaba, Kayo	<b>GES-1</b>
Iga, Shoko	<b>P3-108</b> , P3-200	Inaba, Masaaki	W60-2, P1-251
Igarashi, Hideya	<b>P1-006</b> , P1-026	Inaba, Yutaka	P1-110, P2-133
Igarashi, Toru	P1-025, <b>P3-217</b> , P3-219	Inagaki, Katsunori	<b>MTE2</b> , W18-3, W75-1, P1-028
Igarashi, Toshihisa	W32-5	Inagaki, Masako	W68-3, P3-085
Ihara, Koji	P3-066	Inamura, Ayako	<b>P3-261</b>
Ihata, Atsushi	W32-5, W35-2, <b>W37-5</b> , W67-3, <b>P1-049</b> , P1-074, P3-211	Inayama, Mami	P2-240
Ihn, Hironobu	<b>MTE9</b>	Innami, Kyoko	P2-261
Iida, Hirokazu	W75-4, P2-126	Ino, Rie	P2-266
Iida, Mami	P3-229	Inokuchi, Shoichiro	W17-1, W17-4, W20-4, W64-5, P1-210
Iida, Satoshi	P2-095	Inokuma, Shigeo	SW2-6, W6-3, W23-1, W67-6, P1-206, P1-223, P2-246
Iizuka, Akira	<b>W40-2</b> , P1-168	Inomata, Hirotake	ICW-C4-4, ICW-C9-4, W12-2, W34-6, P1-022, P2-203
Iizuka, Mana	ICW-B4-5, ICW-B5-4, W40-4, W62-1, P2-011	Inoo, Masayuki	P2-032
Iizuka, Nobuko	P2-161, <b>P3-203</b>	Inoue, Asuka	ICW-B1-2, <b>ICW-B3-3</b> , ICW-B7-1, W13-2, W21-2, W30-1, <b>W59-5</b> , P1-001, P1-240, P2-031, P2-142, P3-152
Ikari, Katsunori	<b>S9-3</b> , S12-4, ICW-C4-1, W72-1, <b>ACL3</b> , P3-053, P3-055	Inoue, Eisuke	W31-1, W31-3, W31-5, W66-6, W67-5, P2-005, P3-050
Ikeda, Hiroshi	<b>S3-1</b>	Inoue, Hiromasa	W61-1, W61-2
Ikeda, Kei	<b>S10-4</b> , W24-1, W24-6, W50-4, <b>ES12-1</b>	Inoue, Hiroshi	ICW-B3-1, P1-268, P2-099
Ikeda, Keigo	W17-6, <b>W81-6</b> , P1-233, P2-149, P3-161, P3-201, P3-226	Inoue, Hisashi	W34-2
Ikeda, Shuichi	ICW-B2-1, W9-1, W61-4, P1-166, P3-162	Inoue, Itsuro	<b>S9-6</b>
Ikeda, Takaharu	SW1-5, W21-5	Inoue, Koji	P1-253
Ikeda, Takahide	<b>W35-3</b>	Inoue, Kosuke	W33-2, P1-169, P1-196, P2-196, P3-199, P3-213
Ikegami, Hiroyasu	S12-1	Inoue, Makoto	<b>P2-099</b> , <b>P2-180</b> , <b>P2-192</b> , <b>P3-268</b> , <b>P3-269</b>
Ikegawa, Shiro	<b>S9-2</b>	Inoue, Mamoru	<b>W43-6</b>
Ikegaya, Noriko	W25-3, <b>W25-4</b> , W80-4, P3-046	Inoue, Mariko	S16-4, ICW-B3-6, ICW-B7-3, <b>W17-2</b> , W79-6, P1-103
Ikenaga, Jin	<b>W34-4</b>	Inoue, Miyako	P3-042, <b>P3-044</b> , P3-052, P3-054
Ikenaka, Tatsuoh	P3-247	Inoue, Natsuko	<b>W74-6</b>
Ikenoue, Sumio	P3-058	Inoue, Natsumi	W21-1
Ikeuchi, Hidekazu	W5-4, W29-3, W79-2	Inoue, Ryo	<b>W67-4</b>
Ikezawa, Taiga	P1-220	Inoue, Sanshiro	<b>P1-257</b>
Ikoma, Kazuya	W45-3	Inoue, Satoshi	P2-091
Ikuma, Daisuke	W60-1, <b>W79-2</b> , P2-118, P3-001	Inoue, Yasuo	W72-5
Ikumi, Natsumi	ICW-C4-4, ICW-C9-4, W12-2, W34-6, P1-022, P2-171, P2-203	Inoue, Yasushi	W11-1
Illei, Gabor	W69-6	Inoue, Yoshino	<b>W55-1</b>
Imada, Chiharu	P2-162	Inoue, Yumiko	W8-6, <b>W59-1</b>
Imafuku, Aya	W2-5, <b>W4-6</b> , W21-6	Inoue, Yuzaburo	<b>W75-6</b>
Imagama, Takashi	P1-119, P2-067, <b>P2-088</b>	Inui, Kentaro	W7-4, W30-3, W32-3, W37-1, W38-2, <b>W54-1</b> , W58-2, W58-3, W81-3, W83-3, P1-096, P2-016, <b>P2-063</b> , P2-114, P3-014
Imagawa, Tomoyuki	W9-3	Irimajiri, Shigeo	W56-2
Imai, Atsuko	P3-040, P3-048	Irino, Kensuke	<b>W47-4</b> , P1-126, P1-213
Imai, Hirokazu	W66-5, P2-039	Isbagio, Harry	ICW-C1-4
Imai, Kohzoh	W33-3	Ise, Ayaka	P1-253
Imai, Shinji	P1-107, P2-117	Ishibashi, Mina	W72-1
Imai, Shunichi	<b>W7-5</b> , P1-117	Ishibashi, Yasuyuki	P2-076
Imaizumi, Takahiro	P3-151	Ishida, Hiroshi	<b>W27-6</b>
Imamura, Katsuyuki	W57-4	Ishida, Takaaki	W24-3, <b>W27-1</b>
Imamura, Munetsugu	ICW-C2-4, ICW-C7-2		
Imanaka, Hiroyuki	W26-2, W26-3, W26-6		
Imoto, Kazuhiko	W82-1, P1-229		
Imoto, Yoko	<b>P1-269</b>		
Imura, Shigeaki	P1-048, P1-098, P3-123		
Imura, Yoshitaka	W50-1, W63-6, W65-1		

Ishigaki, Kazuyoshi	ICW-B7-4, ICW-B8-3, W49-4, W83-1, P2-042	Ishizuka, Toshiaki	P1-066
Ishigatsubo, Yoshiaki	ICW-C2-1, ICW-C2-2, W7-2, W8-3, W21-3, W21-4, W64-4, W68-2, W79-3, W80-2, P2-086, P2-159, P2-235, P3-081	Iso, Takenobu	P1-268
Ishigooka, Nozomi	W65-1	Isobe, Masato	P1-031, P2-085, P2-100, <b>P3-260</b>
Ishiguro, Naoki	S18-3, <b>MTE6</b> , SW2-6, <b>SW2-7</b> , ICW-C1-3, ICW-C3-1, ICW-C3-3, W1-1, W1-2, W1-3, W1-4, W1-5, W1-6, W2-2, W2-3, W11-6, W12-3, W12-4, W12-5, W16-2, W16-4, W19-5, W23-1, W23-3, W36-1, W36-2, W36-4, W38-5, W39-6, W57-1, W63-2, W83-6, <b>LS31</b> , P1-043, P1-050, P1-067, P1-069, P1-097, P1-099, P1-100, P1-114, P1-138, P2-004, P2-119, P2-125, P3-012, P3-020	Isoda, Kentaro	W4-1, P2-018, P3-194
Ishihara, Katsuhiko	P1-006, P1-026	Isoda, Yu	P3-153, <b>P3-164</b> , P3-169
Ishihara, Yoshihiro	P1-150	Isojima, Sakiko	W5-6, GES-2, P1-239, P2-023, P2-046, P2-219, <b>P3-086</b>
Ishii, Katsushi	W71-6, <b>P1-092</b>	Isono, Masaaki	W16-6, <b>W32-2</b> , W76-2, P1-047, P1-116, P3-020
Ishii, Koji	P2-162	Isono, Taisuke	<b>P3-181</b>
Ishii, Masaru	ICW-B1-5, <b>LS10-2</b> , <b>ES1-1</b>	Isozaki, Takeo	W18-3, W60-4, P1-028, P2-219, P3-086
Ishii, Nobuyasu	<b>W68-5</b> , P1-246, P3-186, P3-214	Itami, Tetsu	W21-2, W59-5, P1-240, P2-031, P2-142, <b>P3-152</b>
Ishii, Sho	<b>W18-3</b> , P1-028, P1-235, P2-023, P2-148, P2-219, P3-086	Ito, Akinori	<b>P2-108</b>
Ishii, Takao	W10-2, W10-5, W53-3, <b>W53-4</b> , W53-5, P2-130, P3-088	Ito, Haruyasu	W6-5, <b>P1-021</b> , P2-113
Ishii, Tomonori	<b>S1-5</b> , <b>MTE22</b> , ICW-C1-2, ICW-B8-2, W11-5, W65-5, W79-5, P1-243	Ito, Hideki	ICW-C2-3, ICW-C2-4, ICW-C5-4, ICW-C7-2, <b>P3-004</b>
Ishii, Tomoo	S14-3	Ito, Hiroki	W75-2, W83-5, P1-085, P1-120, P2-090, P2-094, P2-096, P3-082
Ishii, Wataru	ICW-B2-1, W9-1, <b>W61-4</b> , P1-166, P3-162	Ito, Hiromu	W30-5, W31-6, W32-4, W39-4, W53-1, W59-3, W63-5, W63-6, W71-3, W71-5, W72-3, W82-3, <b>P1-140</b> , P3-036
Ishijima, Muneaki	S3-1	Ito, Hiroshi	<b>W35-6</b> , W43-4, P2-058, P2-182
Ishikawa, Hajime	W12-1, W15-5, W23-5, W39-1, W45-4, W52-1, W52-3, W63-2, <b>W71-1</b> , W74-1, W83-6, <b>LS20-2</b>	Ito, Katsumi	W2-1, W82-4, P1-145
Ishikawa, Hisato	W23-3, <b>P1-064</b>	Ito, Kazuhiro	<b>P2-233</b>
Ishikawa, Jyunichi	S12-2	Ito, Kiyooki	W4-2, W33-4, W44-6, W60-3, P1-209, P1-242, P2-120, P3-192
Ishikawa, Masahiro	W30-5, W31-6, W32-4, W39-4, W59-3, W63-5, W63-6, W71-3, W71-5, W72-3, W82-3, P1-140, P3-036	Ito, Mari N	<b>W14-5</b> , <b>P2-036</b>
Ishikawa, Yuichi	W43-3	Ito, Naoaki	<b>P3-161</b>
Ishimaru, Hiroyasu	W24-4, P1-172, P2-154, P2-206, P2-207, P2-209, P3-062, P3-071, P3-156, P3-168	Ito, Rei	ICW-C5-1, W49-1, P3-096
Ishimori, Kana	P2-182	Ito, Satoshi	<b>W12-1</b> , W15-5, <b>W23-5</b> , W39-1, W45-4, W52-1, W52-3, W64-1, W71-1, W74-1, <b>LS11</b> , <b>LS15-1</b> , P2-059, P2-102
Ishino, Hidetaka	<b>P3-165</b>	Ito, Shun	<b>W47-6</b>
Ishioka, Eriko	S6-2, <b>P3-207</b>	Ito, Takashi	W24-1
Ishiyama, Kentaro	P3-196	Ito, Takayasu	W1-4, W2-2, W16-2
Ishizaka, Yukihito	P2-020	Ito, Takeya	P1-031, P2-085, P3-260
Ishizaki, Jun	W51-6, P2-252, P3-180	Ito, Tomoki	W82-2, P1-246
Ishizawa, Nobuhiro	W83-5, P1-085, P1-120, P2-090, P2-094, P2-096, P3-082	Ito, Tomoko	W55-2, W68-1, W73-2, <b>W78-2</b>
Ishizu, Akihiro	<b>S15-2</b> , W25-1, W25-2	Ito, Tomoyuki	W33-5, <b>P3-154</b>
Ishizuka, Tatsuo	W35-3, W68-6, P1-191, P3-243	Ito, Yasumasa	<b>P3-139</b>
		Itoh, Daisuke	MTE8
		Itoh, Hirotaka	W2-4, <b>P1-182</b> , <b>P3-087</b> , P3-195
		Itoh, Kenji	W6-1, W19-2, W24-5, P1-014
		Itoh, Yasuhiko	P1-025, P3-217, P3-219
		Itoh, Yasunori	W36-6, <b>P3-111</b>
		Itou, Miyuki	W81-4
		Itou, Yasunori	P3-100
		Iura, Hirotaka	W40-6, P1-142, <b>P3-131</b> , P3-134, P3-140
		Iwahashi, Mitsuhiro	<b>P1-070</b> , P2-052, P2-077, P2-116, P2-164, P3-047
		Iwahori, Yusuke	<b>W72-2</b> , P3-057
		Iwai, Yuka	MTE8
		Iwakura, Mikako	W67-2, P1-153, P1-189, P1-205,

Iwamoto, Itsuo	P2-141 W24-1, P1-109, P1-248	Kadono, Yuho	<b>P1-104</b> , P1-146, P2-033, P2-034 <b>W2-1</b> , W29-5, W54-4, W76-1, P2-055, P3-129
Iwamoto, Masahiro	W3-1, W21-3, W59-4, P3-198	Kadoya, Masatoshi	<b>W66-3</b> , P1-161, P2-110, P3-187
Iwamoto, Naoki	ICW-C8-1, <b>W20-1</b> , W33-1, W34-4, <b>W37-6</b> , W41-5, W64-6, P1-061, P1-160, P2-045, P2-048, P2-205, P3-006, P3-094, P3-238	Kagami, Shin-ichiro	P1-109, P1-248
Iwamoto, Takuji	<b>S12-1</b>	Kagawa, Hideo	W82-2, P3-040, P3-048
Iwamoto, Yukihide	P3-121	Kagawa, Hidetoshi	<b>W79-4</b> , <b>P1-158</b> , P1-201, P1-238
Iwanaga, Nozomi	W9-6, W22-6, W66-2, P2-210, P3-182, P3-259	Kageyama, Goichi	W13-6, W17-5, W34-1, P1-008, <b>P2-143</b> , P2-160, P3-208
Iwanami, Keiichi	<b>P2-040</b>	Kagitani, Maki	<b>P3-120</b>
Iwao, Haruka	ICW-C8-4, P1-208, P2-225	Kai, Motokazu	W42-5, W46-6
Iwasaki, Norimasa	<b>S12-2</b> , W58-5	Kai, Yasufumi	W54-5, P1-072, P1-078, <b>P2-121</b> , P3-090
Iwasaki, Tsuyoshi	W12-6, P3-205	Kaieda, Shinjiro	<b>ICW-B3-2</b> , W9-2, P1-175, P2-231
Iwasaki, Yukiko	S16-4, ICW-B3-6, ICW-B7-3, ICW-B8-3, W17-2, W28-1, W66-1, W79-6, W83-1, P1-260, P2-042	Kaieda, Tomoe	W56-4, P1-121, <b>P1-247</b>
Iwasaki, Yuriko	W81-4	Kajiura, Mikiko	W23-6, W54-6
Iwasaku, Yumi	<b>W5-3</b>	Kajiwara, Mamiko	W25-6, P1-197
Iwasawa, Mitsuyasu	W10-1, W71-4	Kajiyama, Hiroshi	ICW-B1-4, W13-4, W60-1, W79-2, P1-173, P1-212, P1-249, P2-007, P2-118, <b>P3-001</b>
Iwase, Hiroaki	P2-049	Kakuchi, Yasushi	S14-3
Iwata, Hidetoshi	P2-084, P3-136	Kameda, Kazuo	W25-5
Iwata, Kanako	W2-1, P1-183, P1-241, P2-247, P3-018, <b>P3-112</b> , P3-247	Kakegawa, Tetsuji	W3-2, W50-3, W77-6, P2-111, P2-216, P3-070, P3-173, P3-176, P3-178
Iwata, Mitsuhiro	W12-2, P1-022, P2-171, P2-203	Kaku, Yu	W67-4
Iwata, Mitsuru	ICW-C9-4	Kakuchi, Yasushi	W73-4, <b>P2-098</b> , P2-115, P2-147, P3-035, P3-239
Iwata, Naomi	<b>W26-1</b> , W26-5	Kameda, Kazuya	W56-1
Iwata, Noriko	P2-265, <b>P3-257</b>	Kameda, Toshikazu	P1-137, P3-065
Iwata, Satoshi	W79-5	Kamata, Yasuyuki	W59-4
Iwata, Shigeru	ICW-B8-1	Kamba, Yusuke	<b>W58-1</b>
Iwata, Takahiro	W39-4, <b>W71-3</b> , <b>W71-5</b> , P1-140, P3-036	Kameda, Hideto	ICW-C2-3, ICW-C2-4, ICW-C5-4, ICW-C7-2, <b>LS25</b> , <b>ES7-2</b> , P3-004
Iwata, Yasunori	P1-203, P2-156	Kameda, Sadahiko	<b>P3-059</b>
Izumi, Keisuke	<b>ICW-C4-3</b> , ICW-C5-4, W28-5, W76-4, W76-5, P2-140	Kameda, Tomohiro	W9-4, W28-4, W33-6, W34-3, W61-6, W65-6, <b>P1-009</b> , P1-237, P3-222
Izumi, Mayuko	W70-2, W70-3, W78-5, P1-186, <b>P1-202</b>	Kamei, Yuiko	W34-1, P2-160, P3-208
Izumi, Yasumori	W9-6, W66-2, P2-210, P3-182, P3-259	Kamijo, Yuji	W25-5
Izumihara, Tomomaro	W7-1, W56-4, P2-050, <b>P2-052</b> , P3-047	Kamikawa, Teppei	<b>P3-160</b>
Izumikawa, Miharuru	<b>W9-4</b> , W28-4, W33-6, W34-3, W61-6, W65-6, P1-009, P1-237, P3-222	Kamimura, Daisuke	W20-2
<b>J</b>		Kamishima, Tamotsu	<b>S10-5</b> , <b>MTE19</b> , <b>ICW-C2-5</b> , ICW-C2-6, <b>ICW-B4-6</b> , <b>ICW-B4-7</b> , W19-3, W57-3, P2-051, P3-025, P3-118
Jayne, David	W24-1	Kamiya, Masato	P3-100
Jibatake, Akira	W38-4, W70-6, W74-2, <b>P1-204</b> , P2-060, <b>P2-212</b> , P3-075, P3-092, P3-093, P3-236	Kamiyama, Reikou	ICW-C2-1, ICW-C2-2, W7-2, W8-3, W21-4, W32-5, <b>W64-4</b> , W79-3, W80-2, P2-235
Jojima, Hiroshi	P3-270	Kamo, Keiji	W83-5, P1-085, P1-120, P2-090, P2-094, P2-096, P3-082, P3-137
Jouyama, Kazuo	W27-2, P2-105, <b>P3-034</b>	Kamogawa, Yukiko	ICW-B8-2, W65-5
Ju, Ji Hyeon	ICW-B6-5	Kamura, Satoshi	W40-6, P1-142, P3-128, P3-131, <b>P3-134</b> , P3-140
Juji, Takuo	W2-1, W82-4, P1-145	Kanagawa, Hiroya	P1-258
<b>K</b>		Kanai, Yoshinori	W3-3, W55-2, <b>P1-093</b> , P3-028, P3-043
Kaburaki, Makoto	W28-6, W42-1, W59-2, W76-6,		



Kaname, Shinya	W25-3, W25-4, W44-5, W80-4, P1-058, P3-046, P3-197	Karasawa, Hiromi	ICW-C9-4, W12-2, P2-171, P2-203
Kanamono, Toshihisa	W6-3, W67-6, P2-004	Kariya, Yumi	P1-156
Kanaoka, Miwa	P1-151	Karube, Miho	W25-3, W25-4, W80-4, <b>P1-058</b> , P3-046
Kanaya, Fuminori	P3-231	Kasagi, Tomomichi	P2-039
Kanayama, Yasuhide	<b>W1-4</b> , W2-2, W2-3, W11-6, W16-2, <b>W16-4</b> , W36-1, W36-2, W36-4, W38-5, W57-1, P1-067, P1-069, P1-097, P1-099	Kasahara, Akiko	P3-153
Kanazawa, Hiroshi	P1-080, <b>P1-214</b> , <b>P3-097</b>	Kasahara, Hideki	<b>W8-5</b> , W56-6
Kanazawa, Mamoru	P1-119	Kasahara, Yuto	W46-5, P2-193, P3-218, <b>P3-227</b>
Kanazawa, Nobuo	W21-5	Kasai, Yoshiaki	ICW-B3-1
Kanazawa, Satoshi	<b>P1-002</b>	Kasama, Tsuyoshi	W5-6, W18-3, W60-4, GES-2, P1-028, P1-235, P1-239, P2-023, P2-046, P2-148, P2-219, P3-086
Kanbe, Katsuaki	<b>W72-5</b>	Kashihara, Naoki	P3-235
Kanbori, Masayoshi	W23-2, P3-076	Kashihara, Yuko	<b>P2-242</b> , P3-166, <b>P3-244</b>
Kanda, Hiroko	ICW-C5-6, ICW-B3-4, ICW-B9-3, W75-5, W83-1, P2-042	Kashiwado, Yusuke	W51-2, <b>W73-4</b> , P1-065
Kanda, Hiroyasu	W2-2, W16-2, W16-4, W29-1, W42-6, W73-6, W74-4, P1-050, P1-067, <b>P1-069</b> , P1-100, P1-114	Kashiwagura, Takeshi	W75-2, W83-5, P1-085, P1-120, P1-149, P2-090, P2-094, P2-096, <b>P3-027</b> , P3-029, P3-082
Kaneko, Atsushi	W1-4, W2-2, W2-3, W11-6, W12-3, W12-5, W16-2, W16-4, W23-3, <b>W29-1</b> , W36-1, W36-2, W36-4, W38-5, <b>W42-6</b> , W70-5, <b>W73-6</b> , <b>W74-4</b> , <b>LS6-1</b> , <b>LS22</b> , <b>LS28-2</b> , P1-050, P1-067, P1-069, P1-099, P1-100, P1-114, P2-007, P2-251, P3-001	Kashiwakuma, Daisuke	W24-1, P1-109, <b>P1-248</b>
Kaneko, Haruka	S3-1	Kashiwagai, Satoshi	<b>P2-263</b>
Kaneko, Hiroshi	W22-1, W50-2, W74-3, <b>P1-123</b> , P2-222, P3-157	Kassai, Yoshiaki	ICW-B5-7, ICW-B9-2, W13-5, W14-1, W62-2, <b>W62-3</b>
Kaneko, Hirotaka	P1-261	Kasukawa, Yuji	W75-2
Kaneko, Kaichi	W28-6, W42-1, W59-2, W76-6, P1-104, P1-146, P2-033, P2-034, P2-191	Katada, Yoshinori	S6-4, <b>ICW-C4-6</b> , P1-226, P2-174, P2-228, P3-204
Kaneko, Kayoko	GES-3, P2-019, <b>P2-106</b>	Katagiri, Akira	P3-196
Kaneko, Mayumi	<b>W82-6</b> , <b>P1-060</b>	Kataoka, Hiroshi	<b>ICW-B6-1</b> , P2-243
Kaneko, Motohide	P1-033	Kataoka, Ikuho	W25-4
Kaneko, Shunta	<b>W14-2</b> , W40-2, W40-4, W49-2, W49-3, W55-3, P1-019, P3-039	Kataoka, Sayuri	W48-2, W65-3
Kaneko, Tetsuya	P1-136, P1-268, P2-099, <b>P3-013</b>	Kataoka, Yoichi	W83-5, P1-085, P1-120, P2-090, P2-094, P2-096, P3-082
Kaneko, Utako	<b>P3-221</b>	Katayama, Kou	ICW-B4-6, <b>W19-3</b> , <b>W57-3</b> , <b>P2-051</b> , P2-116, <b>P3-025</b> , <b>P3-118</b>
Kaneko, Yoriaki	W5-4, W29-3	Katayama, Masaki	<b>W2-4</b> , W6-3, W67-6, P1-182, P3-087, P3-195
Kaneko, Yuko	ICW-C4-2, ICW-C4-3, ICW-B3-1, ICW-B5-7, W8-6, W31-4, W59-1, <b>P2-044</b>	Katayama, Masao	<b>W29-6</b> , W64-1, W74-4, P2-001, P2-002, <b>P2-009</b> , P2-179, P2-197, P3-188
Kanesaki, Katsuya	ICW-B3-2, W7-1	Katayama, Michihito	ICW-C4-6, <b>W20-5</b> , <b>P1-193</b>
Kaneshiro, Kenta	<b>W18-2</b> , P1-007	Kato, Daisuke	W74-2
Kaneshiro, Shoichi	P1-135, <b>P2-079</b> , <b>P2-122</b>	Kato, Hiroyuki	<b>EL2</b> , P3-145
Kaneshita, Shunya	P2-229, P3-003, P3-220	Kato, Hisamune	<b>W46-1</b>
Kanno, Hiromasa	<b>P3-138</b>	Kato, Kazunori	W68-1, W78-2
Kanno, Seiji	P3-263	Kato, Kenichi	W44-2, P1-178, P3-080, P3-183
Kanno, Takashi	P3-252	Kato, Makoto	S3-2
Kano, Toshikazu	W50-2, P1-123, P3-157	Kato, Masaru	W11-4
Kanzaki, Takehito	W40-5	Kato, Norihiko	W30-6
Kanzawa, Yohei	P2-208	Kato, Rika	ICW-B3-4, ICW-B7-4, <b>ICW-B9-3</b> , W28-1
Kapoor, Mohit	ICW-B2-3, ICW-B5-1, ICW-B5-2, ICW-B5-3	Kato, Shinichi	W36-3, P2-028
Karahashi, Taro	ICW-C3-2, W38-3	Kato, Takashi	W42-5, W46-6, <b>P1-184</b>
		Kato, Takefumi	W1-4, W2-2, W12-3, W16-4, W36-2, P2-052, P3-047
		Kato, Tomohiro	P1-010, P1-011, P1-012, P1-198, P2-163
		Kato, Yasuhiro	W11-2, P2-057, P2-244
		Katsube, Sadanobu	P1-150
		Katsuda, Rinko	W5-1

Katsumata, Yasuhiro	S1-3, <b>S17-5</b> , W5-5, W48-2, W64-2, W65-3, W77-5, P1-154, P1-155, P1-167, P1-219, P1-244, P2-150, P2-198, P2-217, P3-107	Kawakami, Makoto	W18-1
Katsuragawa, Takao	P2-065, <b>P2-177</b> , P3-237	Kawakami, Misato	<b>P1-183</b> , P1-241, P2-247, P3-018, P3-112, P3-247
Katsuyama, Eri	<b>ICW-C7-4</b> , ICW-C8-2, ICW-C8-3, W4-5, W34-5, W48-4, P2-199, P3-064	Kawakami, Shohei	<b>W34-3</b> , P1-237
Katsuyama, Naooki	P1-068, P1-102	Kawakami, Tamihiro	<b>W25-1</b> , W25-2
Katsuyama, Takayuki	ICW-C7-4, <b>ICW-C8-2</b> , ICW-C8-3, W4-5, W34-5, W48-4, P2-199, P3-064	Kawamitsu, Hisae	W47-6
Kawai, Satoshi	P1-220	Kawamoto, Manabu	W58-4, W64-2, W69-1, W77-3, P1-167, P3-146
Kawabata, Kensuke	P1-145	Kawamoto, Taisei	<b>P2-095</b>
Kawabata, Tomoko	ICW-C7-4, ICW-C8-2, ICW-C8-3, W4-5, <b>W34-5</b> , W48-4, P2-199, P3-064	Kawamoto, Toshio	<b>W3-3</b> , P1-093, P3-028
Kawabe, Akio	ICW-C3-5, ICW-B7-7, W43-3	Kawamura, Seiichi	<b>P3-135</b>
Kawabe, Shinji	W26-1, W26-5	Kawamura, Sumito	<b>P2-139</b>
Kawabe, Yojiro	W22-6, W66-2	Kawamura, Tetsuji	W5-1
Kawada, Masahiro	W2-5, W4-6, W21-6, W78-6, P2-107	Kawanami, Takafumi	ICW-C8-4, P1-208
Kawagishi, Tomoyo	W23-2, P3-076	Kawano, Ayako	P1-156
Kawagiuchi, Yoshiharu	W10-4	Kawano, Hiroshi	P2-255, P2-257
Kawaguchi, Hiroshi	<b>S3-5, MTE5</b>	Kawano, Mitsuhiro	W4-2, W13-3, W21-1, W33-2, W33-4, W33-5, W44-6, W60-3, W62-6, W67-4, P1-209, P1-242, P2-120, P3-181, P3-192, P3-250
Kawaguchi, Hoshimi	ICW-B1-2, ICW-B3-3, ICW-B7-1, W13-2, W49-2, W55-3, <b>P1-001</b>	Kawano, Seiji	ICW-B7-2, W40-3
Kawaguchi, Mayumi	P2-258, <b>P3-251</b>	Kawano, Shinya	P1-187, P2-249
Kawaguchi, Tsuyoshi	P2-151	Kawano, Shotaro	<b>W47-1</b> , W47-2, P2-202
Kawaguchi, Yasushi	S1-3, S1-5, W5-5, W18-5, W21-3, W48-2, W64-2, W65-3, W69-2, W69-3, W77-1, W77-3, W77-5, W78-4, LS13, <b>LS24</b> , P1-154, P1-155, P1-167, P1-219, P1-244, P2-150, P2-198, P2-217, P3-107	Kawano, Yoshifumi	W26-6
Kawaguchi, Yohei	P1-128	Kawasaki, Aya	S15-1, <b>W64-1</b>
Kawahara, Chieko	W66-2	Kawasaki, Makoto	P2-014
Kawahata, Kimito	S4-3, S17-6, ICW-B5-6, W14-4, W40-5, W50-5, P1-039	Kawasaki, Masashi	P2-119
Kawahito, Yutaka	ICW-C3-4, ICW-B1-6, ICW-B7-5, W19-4, W24-2, W27-5, W40-1, W43-6, W56-2, W60-5, <b>ACL7, LS4</b> , P1-236, P2-224, P2-237, P3-067, P3-153, P3-185	Kawasaki, Takahiro	<b>P2-057, P2-061</b> , P2-244
Kawai, Shinichi	<b>EL20</b> , W28-6, W42-1, W59-2, W76-6, P1-104, P1-146, P2-033, P2-034, P2-191	Kawasaki, Taku	P1-107, P2-117
Kawai, Takako	W32-5	Kawasaki, Yoshiko	W18-2, P1-059
Kawai, Tomoki	EL6	Kawase, Aya	P1-253
Kawaji, Hidemi	W55-4, P1-137	Kawashima, Hiroto	<b>P1-109</b> , P1-248
Kawakami, Atsushi	S6-3, S6-6, S10-1, <b>MTE21</b> , ICW-C1-2, ICW-C8-1, W7-1, W9-6, W20-1, W22-3, W31-4, W33-1, W34-4, W37-6, W41-5, W62-4, W64-6, <b>LS9-2</b> , P1-061, P1-063, P1-148, P1-160, P1-218, P2-045, P2-048, P2-205, P2-210, P3-006, P3-026, <b>P3-076</b> , P3-094, P3-182, P3-224, P3-238, P3-259	Kawashima, Mikako	W35-3
Kawakami, Katsuyuki	<b>P3-264</b>	Kawashima, Soko	W25-3, W25-4, <b>W44-5</b>
Kawakami, Kosei	W19-6, <b>P2-129</b> , P3-055	Kawashiri, Shin-ya	<b>S10-1</b> , ICW-C8-1, W7-1, W22-6, <b>W33-1</b> , W34-4, W37-6, W41-5, W64-6, P1-061, P1-160, P2-045, P2-048, P2-205, P3-026, P3-094, P3-238
		Kawasumi, Hidenaga	S1-3, <b>W48-2</b> , W64-2, <b>W65-3</b> , P1-167, P1-219
		Kawata, Junko	<b>P3-232</b>
		Kawato, Rui	P1-252, P3-005, <b>P3-072</b>
		Kawazoe, Mai	W28-6, W42-1, W59-2, <b>W76-6</b> , P1-104, P1-146, P2-033, P2-034
		Kempe, Kazuo	W80-6
		Kiboshi, Takao	P3-171, <b>P3-242</b>
		Kida, Daihei	W2-2, W12-3, W12-5, W29-1, W36-1, W36-2, W36-4, W38-1, W38-5, W42-6, W73-6, W74-4, P1-050, P1-069, P1-100, P1-114, P2-119, <b>P2-145</b>
		Kida, Takashi	ICW-C3-4, <b>W24-2</b> , W27-5, W60-5, P1-236, P2-237, P3-067, P3-153, P3-185
		Kido, Akira	ICW-C1-5, P1-106
		Kido, Kenji	P1-119
		Kido, Kensuke	P2-091

Kido, Toshiki	<b>P3-150</b>	Kita, Junko	P2-045
Kifune, Masao	P1-119	Kita, Yasuhiko	P3-073
Kijima, Yasufumi	P1-045	Kitada, Kinya	W67-4, P3-192
Kikkawa, Koji	<b>W47-3</b>	Kitagaichi, Mie	<b>P1-015</b> , P1-016, P1-017
Kikuchi, Eigo	W13-1, <b>W42-3</b> , W46-3, P1-216, P2-006, P2-260, P3-233	Kitagawa, Wataru	W66-5
Kikuchi, Hideaki	W47-5, P2-233	Kitagori, Koji	W50-1
Kikuchi, Hiraku	W36-6, P3-100, P3-111	Kitajima, Shinji	P1-203, P2-156
Kikuchi, Hirotochi	<b>S1-6</b> , SW1-3, W6-2, W68-2, <b>W68-4</b> , P1-018, P2-213, P2-218, P2-221, P2-227	Kitakawa, Hirohiko	P3-163
Kikuchi, Jun	<b>ICW-B9-2</b>	Kitamoto, Kazumasa	P3-057
Kikuchi, Katsuhisa	P2-117	Kitamura, Haruko	<b>P3-258</b>
Kikuchi, Masako	W69-3	Kitamura, Koichi	<b>P3-077</b>
Kikuta, Junichi	<b>ICW-B1-5</b>	Kitamura, Noboru	ICW-C4-4, ICW-C9-4, <b>W12-2</b> , W34-6, P1-022, P2-171, P2-203
Kikuta, Shinsuke	W10-5, W53-3, P2-130	Kitano, Akemi	P1-031, P2-085, P2-100, P3-260
Kim, Dam	<b>ICW-C6-1</b>	Kitano, Masayasu	S6-4, <b>W12-6</b> , W41-6, W43-2, W48-1, W56-2, P1-152, P1-171, P2-166, P2-173, P2-175, P3-116, P3-204, P3-205
Kim, Ji Young	ICW-C6-1	Kitano, Sachie	S6-4, W12-6, P3-204
Kim, Ji-Min	<b>ICW-B4-3</b> , ICW-B4-4	Kitaori, Toshiyuki	W6-3, W67-6, P2-092
Kim, Sang-Hyon	ICW-B4-3, <b>ICW-B4-4</b>	Kiyokawa, Shigehito	P2-052, P3-047
Kim, Yoon Soo	<b>W10-3</b>	Kiyonaga, Yasuhiro	P2-162
Kim, Yoon Taek	W8-4, W13-4	Klareskog, Lars	<b>S13-1</b> , <b>ES4-2</b>
Kimoto, Osamu	ICW-C3-2	Kluve-Beckerman, Barbara	W61-4
Kimoto, Yasutaka	W62-5, P1-027	Koarada, Syuichi	W3-4, W37-2, W66-4, <b>P1-087</b> , P1-108, P1-190, P2-168, P2-214, P3-008
Kimura, Eri	W46-4, <b>P2-008</b>	Kobashigawa, Tsuyoshi	W58-4, W69-1, W77-5, P1-154, P2-150, P2-198, <b>P2-215</b> , P2-217, P3-107, P3-146
Kimura, Fumihiko	W6-1, W19-2, W24-5, P1-014	Kobata, Yasunori	S12-5, ICW-C1-5, P1-106, P2-268
Kimura, Makiko	W68-3, P3-085	Kobatake, Keiko	P3-105
Kimura, Naoki	S4-3, <b>ICW-B5-6</b> , W50-5	Kobayakawa, Tomonori	W11-6, W12-4, <b>W36-1</b> , W38-5, P1-114, P3-012
Kimura, Noriko	<b>P1-077</b>	Kobayashi, Akiko	W31-1, W31-3, W31-5, W66-6, W67-5, P2-005, P3-050
Kimura, Tomoatsu	EL18, W10-4, W36-3, ES6-2, ES12-2, P3-106, P3-132	Kobayashi, Atsushi	W18-5, P2-184, P2-232
Kimura, Yoshitaka	SW1-3, W68-4, <b>P1-018</b>	Kobayashi, Daisuke	W12-1, <b>W15-5</b> , W23-5, W39-1, W45-4, W52-1, W52-3, W71-1, W74-1, P2-102
Kimura, Yuko	P1-165, <b>P2-027</b> , P2-123	Kobayashi, Hiroko	P2-185, P2-211, P3-030, P3-184
Kingetsu, Isamu	W6-5, W49-5, P2-113	Kobayashi, Hiroshi	W18-6
Kinjo, Noriko	P3-215	Kobayashi, Hitoshi	<b>W9-5</b> , P1-124, P2-153, P2-169
Kinoshita, Eri	W83-1, P2-042	Kobayashi, Ichiro	<b>W6-4</b> , W51-5
Kinoshita, Gouki	W10-2, W10-5, W53-3, W53-4, P2-130, P3-088	Kobayashi, Keiko	<b>W30-6</b>
Kinoshita, Katsuhiro	P3-141	Kobayashi, Kenji	<b>P3-106</b>
Kinoshita, Koji	W21-2, W59-5, P1-240, P2-142, P3-152	Kobayashi, Koji	W32-5, W35-2, W37-5, <b>W67-3</b> , P1-049, P1-074, <b>P3-211</b>
Kirino, Yohei	<b>S9-1</b> , ICW-C2-1, ICW-C2-2, W7-2, W8-3, <b>W21-3</b> , W21-4, W32-5, W68-2, W79-3, W80-2, P2-235	Kobayashi, Kumiko	P2-057, P2-061, P2-244, P3-044, P3-054
Kise, Takayasu	W13-1, W42-3, W46-3, P1-216, P2-006, P2-260, <b>P3-233</b>	Kobayashi, Masaki	P1-128
Kishi, Jun	P2-255, P2-257	Kobayashi, Moto	W75-2, W83-5, P1-085, P1-120, P2-090, <b>P2-094</b> , P2-096, P3-027, P3-082
Kishida, Dai	ICW-B2-1, <b>W9-1</b> , W61-4, P1-166, P1-250, P2-155	Kobayashi, Satomi	<b>W49-4</b> , W67-1, W80-5, P2-066
Kishida, Yuki	W46-2, W57-2, <b>P3-234</b>	Kobayashi, Satsuki	P3-105
Kishimoto, Daiga	ICW-C2-1, ICW-C2-2, W7-2, W8-3, W21-4, W32-5, W64-4, <b>W79-3</b> , W80-2	Kobayashi, Shigeto	S5-4, S5-6, S15-1, W34-2
Kishimoto, Kazuya	W21-2, W59-5, P1-240, P2-031, P2-142, P3-152	Kobayashi, Shoko	P1-206, P1-223, P2-246
Kishimoto, Mitsumasa	<b>S5-4</b> , S5-6, SW1-1, W30-2, W37-3, <b>LS5</b> , P2-229, P3-003, P3-220, P3-261		
Kishimoto, Yuji	<b>P2-053</b> , <b>P2-054</b>		

Kobayashi, Tatsuya	<b>P1-122</b> , P3-078	P1-043, P1-050, P1-067, P1-069,
Kobayashi, Tetsuo	<b>P2-102</b>	P1-097, P1-099, P1-100, P1-114,
Kobayashi, Tsutomu	P1-136	P1-138, P2-004, P2-119, P2-125,
Kobayashi, Yoshimichi	P1-040	P3-012, P3-020
Kobayashi, Youhei	S3-1	Kokuzawa, Ayako
Kobori, Kaori	ICW-C3-2, W38-3, <b>W54-3</b>	<b>W59-4</b> , P3-198
Kobori, Makoto	W54-3	Kolling, Christoph
Kobuna, Mika	P1-206, <b>P1-223</b> , P2-246	ICW-B6-3
Kochi, Yuta	W83-1, P2-042	Komagamine, Masataka
Kodama, Kako	<b>W22-2</b> , W48-3, W78-1, P1-157	W81-2
Kodama, Kunihiro	W56-4	Komagata, Yoshinori
Kodama, Satoru	W12-1, W15-5, W18-5, W23-5, W45-4, W52-1, W52-3, W71-1, <b>W74-1</b> , P2-184, P2-232	<b>S15-5</b> , W25-3, W25-4, W44-5, W80-4, P1-058, P3-046, P3-197
Kodama, Shoko	W3-2, W50-3, <b>W77-6</b> , P2-111, P2-216, P3-070, P3-173, P3-176, P3-178	P1-253
Kodama, Tatsuhiko	<b>S7-5</b>	Komai, Koichiro
Kodera, Takao	ICW-C1-2, <b>P3-174</b>	Komai, Toshihiko
Koenuma, Naoko	W19-6, P2-129, P3-055	<b>S16-4</b> , ICW-B3-6, W17-2, W28-1, <b>W79-6</b>
Koga, Takuma	<b>P2-231</b>	Komatsu, Noriko
Koga, Tomohiro	<b>ICW-C1-2</b> , ICW-C8-1, W22-6, W33-1, W34-4, W37-6, W41-5, W64-6, P1-061, P1-160, P1-218, P2-045, P2-205, P3-094, P3-238	Komatsu, Rie
Kogata, Yoshinori	W13-6, W17-5, W34-1, P2-143, P2-160, P3-208	Komatsu, Shuichi
Kogawa, Masakazu	<b>ICW-C6-3</b>	Komine, Mitsunori
Kogure, Toshiaki	P2-064	Komistek, Richard
Kohno, Johji	ICW-C4-6, P2-228	W53-1
Kohno, Masataka	ICW-C3-4, ICW-B1-6, ICW-B7-5, W24-2, W27-5, W40-1, W60-5, P1-236, P2-237, P3-067, P3-153, P3-185	Komiya, Akiko
Kohsaka, Hitoshi	S4-3, S17-6, ICW-B5-6, W14-4, W50-5, P1-039	W13-1, P1-183, P1-241, P2-056, P2-059, P2-247, P3-018, P3-112, <b>P3-247</b>
Koido, Norihiko	P3-007, P3-040, P3-048	W57-4
Koike, Ryuji	S4-3, W29-2, W31-4	P3-230
Koike, Takao	<b>SW2-2</b> , ICW-C2-5, W1-1, W1-2, W1-3, W1-5, W1-6, W8-5, <b>W23-1</b> , W29-2, W56-6, SW2-6	W18-5, <b>P2-184</b> , P2-232
Koike, Tatsuya	W7-4, W30-3, W32-3, W37-1, W38-2, W54-1, W58-2, W58-3, W81-3, W83-3, <b>ES7-1</b> , P1-096, P2-016, P2-063, P2-114, P3-014, P3-061, P3-144	W44-3, <b>W80-6</b> , P1-017, P1-162, P2-025, P2-047
Koiwa, Masahito	P1-137, P3-065	P2-057, P2-061, P2-244
Koizumi, Hideki	P1-012	W77-5, <b>P2-217</b>
Koizumi, Yasuhiko	W2-1	W34-3, <b>P1-237</b>
Koji, Hitoshi	W25-4	P2-091
Koji, Takehiko	W62-4	W18-1, P1-188, <b>P2-146</b> , P3-202, P3-267
Kojima, Masayo	W63-2, <b>W83-6</b>	P3-040, P3-048
Kojima, Toshihisa	S18-3, ICW-C1-3, ICW-C3-1, ICW-C3-3, W1-4, W2-2, W2-3, W11-6, W12-3, W12-4, W12-5, W16-2, W16-4, W19-5, W23-3, W36-1, <b>W36-2</b> , W36-4, W38-5, W39-6, W57-1, <b>W63-2</b> , W83-6,	P2-257
		<b>ICW-C6-4</b> , <b>ICW-B7-6</b> , W2-6, W41-1, W57-6, P1-038, P1-045, P1-133, <b>P2-083</b> , <b>P3-127</b> , <b>P3-142</b>
		ICW-C7-3, <b>W16-1</b> , W76-3, P1-033, P1-062, P1-115, P3-262
		<b>ICW-B3-1</b> , <b>W8-6</b>
		S6-6, ICW-B4-5, ICW-B5-4, W13-2, W14-2, W28-3, W40-2, <b>W40-4</b> , W49-2, W49-3, W55-3, W62-1, W64-1, P1-019, P1-030, P1-032, P3-039
		<b>W65-1</b>
		<b>P2-243</b>
		W75-2, W83-5, P1-085, P1-120, P1-149, P2-090, P2-094, P2-096, P3-082, <b>P3-137</b>
		P3-190, P3-242
		ICW-C4-6, P1-226, P2-174, P2-228
		<b>EL16</b> , <b>SW1-3</b> , ICW-B6-1, W2-1, W6-2, W64-1, W68-4, P1-018, P2-213, P2-218, P2-221, P2-227
		P1-185, P2-170
		W22-1, W50-2, <b>P3-157</b>
		<b>ICW-C2-6</b> , ICW-B4-7, W11-4, W47-5, P2-233
		Kono, Hiroki
		Kono, Masanori
		Kono, Michihito
		Konaka, Hachiro
		Konda, Naoko
		Kondo, Atsushi
		Kondo, Hiromi
		Kondo, Masahiro
		Kondo, Masakazu
		Kondo, Mayo
		Kondo, Naoki
		Kondo, Tsuneo
		Kondo, Yasushi
		Kondo, Yuya
		Kondo-Ishikawa, Seiko
		Kondou, Makoto
		Konishi, Natsuo
		Konma, Junichi
		Konma, Kazushi
		Kono, Hajime

Konta, Tsuneo	P1-141, P1-159	P1-008, P1-186, P1-202, P2-143, P3-068
Koo, Malcolm	ICW-C4-5	
Kosaka, Nami	P2-261	Kumagaya, Shinichiro <b>S18-6</b>
Kosuge, Lisa	<b>P2-201</b>	Kumano, Kotaro W43-5, P3-223
Kosugi, Shinji	<b>EL11</b>	Kumanogoh, Atsushi <b>S16-1, IS2-2</b> , ICW-B4-2, W11-2, W20-5, P1-193, P1-255
Kotake, Shigeru	<b>W58-4</b> , W69-1, P2-215, P3-146	
Kotani, Akihiro	S14-3	Kume, Kensuke P2-052, P3-047
Kotani, Takuya	W24-3, W27-1, W27-4, W80-3, P2-152, P2-189, P2-245, P3-212, P3-240	Kumon, Yoshitaka S5-6, <b>P1-228</b>
		Kunibu, Akinori W60-1, P1-249
Koto, Aya	W47-1, <b>W47-2</b> , P2-202	Kunimatsu, Junwa W59-6, <b>P1-250</b>
Kotsuma, Tatsuo	P3-040, P3-048	Kunishita, Yosuke ICW-C2-1, ICW-C2-2, W7-2, W8-3, W21-4, <b>W32-5</b> , W79-3, W80-2, P2-235
Kowata, Kouko	W9-5, P1-124, P2-153, P2-169	
Koyama, Kensuke	<b>W20-3, W39-3</b> , P2-049	Kunitake, Yukiko ICW-B3-2, W9-2, P1-175, P2-231
Koyama, Natsu	<b>S18-1</b>	Kunizawa, Kyohei P3-197
Koyama, Takuma	W29-5, W54-4, <b>P2-055</b>	Kunou, Miyoko P2-039
Koyama, Yasushi	W16-3, W51-4, P1-112, P1-181, P2-176, <b>P3-158</b> , P3-175	Kurabayashi, Takayoshi W16-3, W51-4, P1-112, <b>P1-181</b> , P2-176, P3-158, P3-175
Koyama, Yoshinobu	W6-3, W67-6, <b>W77-4</b> , P1-065, P3-033, P3-179	Kurasawa, Kazuhiro W55-5, P1-083, P3-109, P3-113, P3-266
Koyano, Satoru	<b>P2-103, P2-104, P2-116</b>	Kurasawa, Takahiko <b>W3-6</b> , W44-4, W73-1
Kozu, Noritsune	P2-118	Kurashima, Yuko <b>ICW-B1-2</b> , ICW-B3-3, ICW-B7-1, W13-2, W28-3, W49-2, W49-3, W55-3, P1-001
Krishnaswami, Sriram	W15-1, W15-3, W15-4	
Kubo, Kanae	W75-5, W83-1, P2-042	Kurata, Izumi W28-3, W49-2, W49-3, P1-030, P1-032
Kubo, Kazuyoshi	W54-5, P1-078, <b>P1-156</b>	
Kubo, Makoto	P1-119	Kurata, Noriyuki P2-032
Kubo, Satoshi	ICW-C1-6, <b>ICW-C3-5</b> , ICW-C9-2, <b>ICW-C9-3</b> , ICW-B1-3, ICW-B6-2, ICW-B8-1, <b>ICW-B9-1</b> , W14-3, W37-4, W38-6, W41-2, W43-3, W49-6, W55-1, W70-4, W77-2, P1-086, P3-015	Kurihara, Yuko <b>P2-161</b> , P3-203
		Kurusu, Rina W62-3
Kubo, Toshikazu	ICW-B7-5, W7-6, W19-4, W27-5, W40-1, W45-3, W60-5, W72-4, P2-224, P2-237, P3-016, P3-126, P3-185	Kurisuno, Makoto W72-2, <b>P3-057</b>
		Kuritani, Taro P3-042, P3-052
Kubota, Ayako	<b>W39-2, W63-4</b> , GES-3, <b>P1-041</b> , P1-103	Kuroda, Hiroshi W54-5, P1-072, P1-078, P2-121, P3-090
Kubota, Isao	P1-159	Kuroda, Takeshi ICW-C6-4, W2-6, W4-4, <b>W6-6</b> , W41-1, W44-1, W57-6, W61-3, W65-4, W79-1
Kubota, Sayaka	W25-4	
Kubota, Takao	<b>P1-125</b>	Kuroiwa, Takanori W56-2, P3-042, P3-044, P3-045, P3-052, P3-054
Kubota, Tomohiro	<b>W26-2</b> , W26-3, W26-6	
Kubota, Yasuhiro	<b>P1-035</b>	Kurokawa, Manae S. P1-010, P1-011, P1-012, P1-198, P2-163
Kuda, Harumi	<b>W28-5</b> , W76-4, W76-5, P2-140, P3-206, P3-210	Kuroki, Yasuo <b>P2-072</b>
		Kurosaka, Daitaro W6-5, W49-5, P1-021, P2-113
Kudo, Kanako	W75-6	Kurosaka, Masahiro W45-2, P1-040, P1-044, P1-046, P2-080
Kudo, Naoko	W2-6, P1-038, P1-045, P1-133, P2-083	Kurose, Nozomu P1-208
		Kurose, Rie <b>P2-076</b>
Kudo, Takeo	P1-029, P2-165, <b>P2-250</b>	Kurumizawa, Megumi P3-183
Kuga, Yoshiaki	W74-2, P1-033	Kusaka, Yoshiaki P3-041
Kujime, Rie	ICW-C2-4, ICW-C7-2, P3-004	Kusakabe, Torao P2-091
Kukida, Yuji	<b>ICW-C3-4</b> , ICW-B1-6, ICW-B7-5, W24-2, W27-5, W40-1, P1-236, P3-067, P3-153, P3-185	Kusaoi, Makio W64-1, P1-016, P1-017
		Kusayama, Yoshihiro P1-110, P2-133
Kukita, Akiko	W17-1	Kushida, Taketoshi <b>W75-4</b>
Kumagai, Kazuhiko	W14-6, P1-185, P2-170, P3-125	Kushimoto, Kouhei W45-5
Kumagai, Ken	<b>P1-110</b> , P2-133	Kusuda, Takeshi P3-108, P3-200
Kumagai, Shunichi	W41-4, W70-2, W70-3, W78-5,	Kusumoto, Norio P1-156
		Kusunoki, Natsuko W28-6, W42-1, W59-2, W76-6, P2-033, P2-034
		Kusunoki, Norio P3-255

Kusunoki, Yoshie	<b>P3-002</b>	Major, Gabor	ICW-C6-2
Kuwana, Masataka	<b>S1-4, S8-6, EL22, W78-4, LS13, LS33</b>	Maki, Hisataka	W28-1
		Makiishi, Shohei	P1-203, P2-156
		Makino, Hirofumi	S15-1, ICW-C7-4, ICW-C8-2, ICW-C8-3, W4-5, W34-5, W48-4, W79-4, P1-158, P2-199, P3-064
<b>L</b>			W24-3, W27-1, <b>W27-4, W80-3,</b> P1-165, P1-245, P2-027, P2-123, P2-152, P2-172, P2-189, P2-245, P3-051, P3-120, P3-190, P3-212, P3-228, P3-240
Lafyatis, Robert	ICW-B2-5	Makino, Shigeki	W18-5, W74-1, P2-184, P2-232
Lagares, David	<b>ICW-B2-3</b>	Makita, Sohei	W24-6
Lai, Jinzhi	ICW-C7-6	Malmström, Vivianne	<b>S11-1</b>
Lai, Ning-Sheng	<b>ICW-C4-5</b>	Mamoto, Kenji	W7-4, <b>W30-3,</b> W32-3, W37-1, <b>W38-2,</b> W54-1, W58-2, W58-3, W81-3, W83-3, P1-096, P2-016, P2-063, P2-114, P3-014
Lam, Ky	<b>ICW-B9-6</b>		
Lam, Wai Kai	ICW-B9-4	Mamura, Mizuko	<b>ICW-B6-5</b>
Lau, Cs	ICW-B9-6	Mandai, Koji	<b>P3-014,</b> P3-061
Lee, Hae-hyun	P1-084	Mannami, Kenji	P1-088, P3-040, P3-048
Lee, Hyo-Jung	ICW-B4-3, ICW-B4-4	Marrotta, Anthony	ICW-B6-2, W41-2
Lee, Tae-Han	ICW-B4-3, ICW-B4-4	Marshall, K. Wayne	ICW-B5-1
Li, Mengtao	ICW-C7-6, ICW-B2-4, ICW-B8-6, ICW-B9-5	Martel-Pelletier, Johanne	ICW-B5-1
		Marumo, Keishi	P2-223
Li, Yi	P2-021	Marumo, Tomofumi	<b>P2-230</b>
Li, Ying-Hua	ICW-B5-1, <b>ICW-B5-3</b>	Maruoka, Momo	W56-1, P1-171, P3-241
Liang, Matthew H	S17-1	Marutani, Ryushi	W71-4
Liao, Chien-Chang	<b>ICW-C7-1</b>	Maruyama, Akihito	W59-4
Liepnieks, Juris	W61-4	Maruyama, Keisuke	W43-1, P2-112
Lin, Qingshun	<b>W64-3,</b> P2-012, P2-013	Maruyama, Takashi	W8-4, W60-1, <b>P1-249,</b> P2-118
Lin, Shih-Chang	ICW-B8-4	Masago, Yumiko	P1-253
Liu, Fei	ICW-B2-3	Masaki, Yasufumi	<b>ICW-C8-4,</b> P1-208, P2-225
Liu, Yongtai	ICW-C7-6	Masaoka, Toshinori	S14-3
Lo, Y	ICW-B9-6	Masatomi, Takashi	<b>ES10</b>
Lu, Cheng-Hsun	<b>ICW-C7-5</b>	Masuda, Kanako	<b>P2-158</b>
Luk, D	ICW-B9-6	Masuda, Kimio	W10-1, <b>W71-4</b>
Lundberg, Ingrid E	<b>S17-1</b>	Masuda, Toru	W81-5
Luo, Yongting	ICW-B2-4	Masui, Yoshinori	P1-123
		Masuko, Tatsuya	S12-2
<b>M</b>		Masumoto, Junya	ICW-B2-2
Machiayama, Tomoaki	<b>P1-215</b>	Masuoka, Shotaro	<b>W28-6,</b> W42-1, W59-2, W76-6, P1-104, P1-146, P2-033, P2-034
Machida, Takahiro	W39-5, W71-2, P1-129, P1-264, <b>P2-270</b>		W27-2, P2-105, P3-034
Machiyama, Tomoaki	ICW-B8-2, W65-5, P1-243	Matoba, Kenichiro	W18-6
Macias, William	W69-4	Matsubara, Erika	W63-3
Madda, Rashmi	ICW-B8-4	Matsubara, Saburo	W56-1, <b>ACL5,</b> P1-131, P1-132, P2-050, P2-052, P2-103, P2-104, P2-116, <b>P3-040,</b> P3-047, P3-048
Maeda, Akitoshi	<b>P3-041</b>		W9-1
Maeda, Hiroyuki	P2-220	Matsuda, Masayuki	<b>P2-264</b>
Maeda, Junko	<b>W59-6,</b> P1-250	Matsuda, Michiko	P1-156
Maeda, Keiji	W56-2, P3-042, P3-044, P3-052, P3-054	Matsuda, Motohiro	W30-5, W31-6, W39-4, W53-1, W63-5, W71-3, W71-5, W72-3, P1-140, P3-036
Maeda, Shinji	W23-6, W54-6, <b>P3-115,</b> P3-225	Matsuda, Shuichi	W56-4, W57-4, P1-053, P1-121, P1-247
Maeda, Tomoyo	P3-115		W3-3, <b>W55-2,</b> W73-2, P1-093,
Maeda, Toshihisa	W45-2, P1-040, P1-044, <b>P1-046,</b> P2-080	Matsudaira, Ran	
Maehara, Takashi	S6-1		
Maekawa, Makiko	<b>W62-5,</b> P1-027		
Maeshima, Akito	W5-4, W29-3		
Maeshima, Etsuko	<b>P2-254</b>		
Maeshima, Shinichiro	P2-254		
Maesono, Tomohiro	W80-4		
Maeyama, Akira	<b>P3-270</b>		
Maezawa, Reika	W55-5, P1-083, P3-109, <b>P3-113,</b> P3-266		
Mahomed, Nizar N.	ICW-B5-1, ICW-B5-3		

	P3-028, P3-043	Matsunaga, Keiichiro	P1-221
Matsueda, Megumi	P2-258	Matsuno, Hiroaki	<b>LS30-2, ES5-1</b> , P2-050, P2-052, P2-116, P3-040, <b>P3-047</b> , P3-048
Matsueda, Yu	W22-2, W48-3, <b>W78-1</b> , P1-157, P2-074	Matsuo, Hirotaka	ICW-B2-6
Matsuhashi, Megumi	P1-031, <b>P2-085</b> , P2-100, P3-260	Matsuo, Kinue	<b>W45-6</b>
Matsui, Atsushi	W48-6, P2-195, P2-204, P3-150, <b>P3-159</b> , P3-193	Matsuo, Seiichi	S15-1
Matsui, Kazuo	W30-2, W37-3, P2-201, P3-009	Matsuo, Yusuke	<b>W14-4</b>
Matsui, Kiyoshi	S6-4, W12-6, W41-6, W43-2, W48-1, W56-2, W56-3, P1-152, P1-171, P2-166, P2-173, P2-175, <b>P3-116</b> , P3-204	Matsuoka, Hiroshi	P1-033
Matsui, Nobuo	P1-035	Matsuoka, Naoki	W7-1, P2-211, P3-030, <b>P3-184</b>
Matsui, Shoko	W48-6	Matsushita, Hiromi	W35-6, W43-4, P2-058, P2-182
Matsui, Toshihiro	W2-1, W10-1, W29-1, W29-4, W29-5, W31-2, W31-4, W42-6, W54-4, <b>W70-5</b> , W71-4, <b>LS7-2</b> , P1-183, <b>P1-241</b> , P2-007, P2-008, P2-009, P2-055, P2-074, P2-247, P3-001, P3-018, P3-032, P3-112, P3-247	Matsushita, Isao	<b>EL18</b> , W10-4, W36-3, <b>ES6-2, ES12-2</b> , P3-106, P3-132
Matsui, Yuichiro	S12-2	Matsushita, Kakushi	P2-158
Matsui, Yukio	P2-229, P3-003, P3-220	Matsushita, Kazuhiko	<b>S14-3</b>
Matsukawa, Yoshihiro	ICW-C9-4, W12-2, W34-6, P2-171, P2-203	Matsushita, Masakazu	P2-047, P2-249
Matsuki, Yuko	P2-025, P2-047	Matsushita, Masato	ICW-C4-6, W16-5, W31-2, W32-1, W54-2, <b>P1-127</b> , P2-024, P2-241
Matsukura, Noboru	P3-100	Matsushita, Masatoshi	P1-268
Matsumiya, Ryo	W18-6	Matsushita, Tetsunao	P2-078
Matsumoto, Ami	P1-124, P2-153, <b>P2-169</b>	Matsusue, Yoshitaka	P1-107, P2-117
Matsumoto, Hirotoshi	P1-220	Matsuura, Miyuki	P3-256
Matsumoto, Isao	S6-6, S11-4, <b>EL26</b> , ICW-B1-2, ICW-B3-3, ICW-B4-5, ICW-B5-4, ICW-B6-5, ICW-B7-1, W13-2, W14-2, W28-3, W40-2, W40-4, W49-2, W49-3, W55-3, W62-1, W64-1, P1-001, P1-019, P1-030, P1-032, P1-168, P2-011, P3-039	Matsuura, Takanori	<b>P2-014</b>
Matsumoto, Kotaro	W38-4, W70-6, W74-2, <b>P2-060</b> , P3-075, P3-092, <b>P3-093</b> , P3-236	Matsuura, Yoshinobu	<b>W11-2</b>
Matsumoto, Mitsuyo	P1-066	Matsuyama, Takami	P1-053
Matsumoto, Risa	W71-6, P1-092	Matsuyama, Takeshi	P3-217
Matsumoto, Soichi	SW1-4	Matsuyama, Yukihiro	W38-3
Matsumoto, Takayuki	P3-105	Mawatari, Masaaki	P2-131
Matsumoto, Takeshi	W2-1	McInnes, Iain	<b>S13-3, ES8-1</b>
Matsumoto, Takumi	<b>P2-065</b> , P2-177, P3-108, <b>P3-200</b> , P3-237	McInnes, Iain B	<b>ICW-C9-6</b>
Matsumoto, Takuya	W12-4, W51-6, <b>P2-252, P3-012</b> , P3-180	Mease, Philip	ICW-C9-6
Matsumoto, Tatsuki	W33-2, P1-169, P1-196, P2-196, P3-199, <b>P3-213</b>	Mengtao, Li	ICW-C9-1
Matsumoto, Tomoshige	<b>P3-084</b>	Mibe, Junya	<b>W72-6</b>
Matsumoto, Yoshihiro	P1-024, P2-010	Michaels, M. Alex	W69-5
Matsumura, Itaru	W21-2, W30-1, W59-5, P1-240, P2-031, P2-142, P3-152	Michel, Beat A	ICW-B6-3
Matsumura, Masami	W21-1	Michinoku, Tocilizumab Study Group	W11-5
Matsumura, Noboru	S12-1	Michishita, Kazuya	W40-5
Matsumura, Ryutarō	P1-179, P2-003, <b>P3-083</b>	Miday, Robert	W69-6
Matsumura, Yoko	P3-051	Migita, Kiyoshi	W7-1, W9-2, W9-5, <b>W9-6</b> , W22-3, W37-6, W61-5, <b>W66-2</b> , P1-251, P1-252, P2-059, P2-210, P3-182, P3-259
		Mikage, Hidenori	W35-6, P2-182
		Mikami, Hiroshi	P2-238, P3-149
		Mikawa, Yoshihiro	W58-1
		Miki, Kenji	W56-2, P3-045, P3-100
		Miki, Miyuki	ICW-C8-4, P1-208, P2-225
		Miller, Frederick W	S17-1
		Mima, Noriaki	P1-118
		Mimori, Akio	W22-1, W50-2, W74-3, P1-123, P2-020, P2-222, P3-157
		Mimori, Tsuneyo	W23-1, W30-5, W31-6, W32-4, W39-4, W41-6, W48-1, W50-1, W51-3, W59-3, W63-5, W63-6, W65-1, W71-3, W71-5, W82-3, <b>LS18</b> , P1-140, P3-036
		Mimura, Toshihide	<b>S4-5</b> , ICW-B1-4, W8-4, W13-4, W60-1, W79-2, P1-033, P1-173, P1-212, P1-249, P2-007, P2-026,

	P2-118, P3-001	Miyagi, Kenichi	W7-2
Min, Chisun	SW1-1, P2-229, <b>P3-003</b> , P3-220	Miyagi, Rumiko	W32-5, <b>P2-159</b> , P3-081
Minami, Akio	S12-2	Miyahara, Hisaaki	W40-6, W63-2, W83-6, P1-142, P3-128, P3-131, P3-134, P3-140
Minami, Michio	P2-052, P2-139, P3-047		W36-4, W38-1, W38-5
Minami, Rumi	W3-2, W50-3, W77-6, P2-111, P2-216, P3-070, P3-173, <b>P3-176</b> , P3-178	Miyake, Hiroyuki	P3-270
		Miyake, Katsuhisa	W5-1, P1-154
Minami, Shinji	P3-263	Miyake, Kohei	P2-052, P3-047
Minato, Yoshiaki	P3-141	Miyake, Nobumasa	<b>S16-5, IS2-5, EL9</b> , GES-3, P1-015, P1-016, P1-017
Minatoguchi, Shun	<b>P1-252</b> , P3-005, P3-072	Miyake, Sachiko	W75-2, W83-5, P1-085, P1-120, P1-149, P2-090, P2-094, P2-096, P3-027, P3-029, P3-082, P3-137
Mine, Takatomo	P1-119, P1-143		GES-3, P3-217
Minegishi, Kaoru	<b>ICW-C2-1</b> , ICW-C2-2, W7-2, W8-3, W21-4, W32-5, W79-3, W80-2, P2-235	Miyakoshi, Naohisa	<b>P1-259</b> , P3-263
			<b>P2-267</b>
Minegishi, Youjiro	P2-089, P2-093	Miyamae, Takako	W75-2, <b>W83-5, P1-085</b> , P1-120, P1-149, P2-090, P2-094, P2-096, P3-027, P3-029, P3-082, P3-137
Minemura, Nobuyoshi	P2-179, P2-197, P3-188	Miyamoto, Erabu	P2-162
Minoda, Masahiro	<b>W30-2</b> , W37-3, P2-201, P3-009	Miyamoto, Kazuyo	<b>P2-136</b> , P3-023
Minota, Seiji	W3-1, W42-2, W59-4, P1-054, P1-199, P2-236, P3-198	Miyamoto, Seiya	<b>IS1-3</b>
			ICW-C3-2, ICW-C5-1, <b>W23-4</b> , W38-3, W49-1, <b>P1-056, P1-071</b> , <b>P1-101</b> , P2-052, P3-047, P3-096, <b>P3-098</b>
Minowa, Kentaro	W55-2, W73-2, <b>P2-025</b> , P2-047	Miyamoto, Shinji	W3-2, W50-3, W77-6, P2-001, P2-002, P2-009, <b>P2-111</b> , P2-216, P3-070, P3-173, P3-176, P3-178
Misaki, Kenta	ICW-C5-2, W3-5, W8-2, W15-6, P1-176, P1-225, P1-265, P2-226, P2-267	Miyamoto, Shuichi	S15-1, ICW-B5-6, W1-1, W1-2, W1-3, W1-5, W1-6, W14-4, W29-2, W31-4
		Miyamoto, Takeshi	W82-2
Mise, Koki	W4-6, W21-6, W48-5, W78-6, P2-107	Miyamoto, Toshiaki	W22-6, P2-210, <b>P3-259</b>
Mishima, Koji	W17-1, W64-5		<b>W17-6</b>
Mishima, Shintaro	<b>W17-3</b>	Miyamura, Tomoya	<b>W70-4</b>
Mito, Takafumi	P2-261		W6-3, W67-6, <b>P2-071</b>
Mitogawa, Takehide	P3-230		P1-156, <b>P2-234</b>
Mitoma, Hiroki	W11-1, W17-1, W17-4, W20-4, W47-1, W47-2, W50-6, W64-5, P2-202	Miyasaka, Nobuyuki	<b>LS8</b>
			W5-2, P1-232, P1-234
Mitomi, Hirofumi	W28-2, W43-4, <b>P2-058</b> , P2-182		ICW-C8-2, ICW-C8-3, W4-5, W48-4, <b>P2-199</b> , P3-064
Mitsugi, Naoto	W71-6, P1-092	Miyashima, Shigeo	P1-036, P1-119
Mitsuhashi, Takashi	<b>P1-088</b>	Miyashita, Taiichiro	ICW-B3-1, ICW-B5-7, ICW-B9-2, W13-5, W14-1, W62-2, W62-3
Mitsui, Hiroto	P1-128	Miyashita, Tomoko	ICW-B2-2, W51-6
Mitsuka, Takeshi	P3-040, P3-048	Miyata, Hiroko	W39-2, W63-4, P1-041
Mitsumoto, Heidai	W45-3	Miyata, Masayuki	W20-6, P1-013
Mitsuzaki, Akio	P1-031, P2-085, P2-100, P3-260	Miyauchi, Shunichi	ICW-B9-1, <b>W14-3</b> , W37-4, W38-6, W43-3
Miura, Takako	W56-1, P2-103, P2-104, P2-116	Miyauchi, Takashi	P1-119
Miura, Yasushi	ICW-B7-2, <b>W45-2</b> , W45-6, P1-040, P1-044, P1-046, <b>P2-080</b> , P3-042, P3-052	Miyawaki, Shoji	W80-4
		Miyawaki, Yoshia	W26-6
Miura, Yoko	W60-4, GES-2, P1-028, P1-206, P1-223, P2-148, <b>P2-246</b> , P3-086		<b>P1-246</b>
		Miyazaki, Noriyuki	W13-1, W42-3, <b>W46-3</b> , P1-216, P2-006, P2-260, P3-233
Miwa, Yusuke	W5-6, W18-3, W60-4, <b>GES-2</b> , P1-028, P1-235, P2-023, P2-046, <b>P2-148</b> , P2-219, P3-086	Miyazaki, Takahiro	W14-4
			W22-6, P3-026
Miya, Masahiko	<b>W63-1</b>	Miyazaki, Tatsuhiko	
Miyachi, Kiyomitsu	W7-2, <b>P1-113, P3-007</b>	Miyazaki, Yoshiyasu	
Miyagawa, Eiko	W67-2, <b>P1-153</b> , P1-189, P1-205, P2-141	Miyazaki, Yumi	
		Miyazaki, Yusuke	
Miyagawa, Ippei	ICW-C1-6, ICW-C3-5, ICW-C9-2, ICW-C9-3, ICW-B6-2, <b>ICW-B6-6</b> , W14-3, W41-2, W43-3, W49-6, W55-1, W70-4, W77-2, P1-086, P3-015	Miyazato, Hajime	
		Miyazawa, Sayaka	
Miyagawa, Taro	P1-203, P2-156	Miyazono, Akinori	
Miyagawa, Yusuke	W47-6	Miyoshi, Tomoki	
		Miyoshi, Yuji	
		Mizoguchi, Fumitaka	
		Mizokami, Akinari	



Mizuki, Shinichi	W6-3, W67-6, W73-4, P2-098, P2-115, P2-147, <b>P3-035</b> , P3-239	Morita, Yoshitaka	ICW-B1-1, ICW-B4-1, W18-4, P1-023, P1-026, P2-261
Mizumoto, Katsutoshi	<b>W18-5</b> , P2-184, P2-232	Moritake, Akihiro	P2-078
Mizuno, Masami	<b>W4-3</b> , P2-167	Moriwaki, Kazuhiko	P3-230
Mizuno, Shohei	P3-253	Moriwaki, Kenta	P2-053, P2-054
Mizuno, Yasushi	<b>P2-208</b>	Moriya, Yuji	P3-143
Mizushima, Ichiro	W13-3, <b>W33-4</b> , W33-5, P3-181, P3-250	Moriyama, Masafumi	<b>S6-1</b> , W62-1
Mizushima, Machiko	W35-6, <b>P1-177</b> , P2-058, P2-182	Moriyama, Mayuko	P1-188, P2-146, <b>P3-202</b>
Mizushima, Kennosuke	ICW-C2-3, ICW-C2-4, ICW-C5-4, ICW-C7-2, P3-004	Moriyama, Michiyo	W74-6
Mizuta, Hiroshi	W63-3	Morooka, Masaaki	P2-087
Mizuuchi, Takahiro	W46-4	Morooka, Takaaki	P2-087
Mochida, Satoshi	<b>EL3</b>	Motohashi, Rena	W29-3
Mochida, Yuichi	<b>MTE14</b> , <b>W71-6</b> , P1-092	Motohashi, Yutaka	W47-3
Mochizuki, Takeshi	S12-1, W19-6, P2-129, <b>P3-055</b>	Motojima, Shinji	W38-4, <b>W70-6</b> , W74-2, P1-204, P2-060, P2-212, <b>P3-075</b> , P3-092, P3-093, P3-236
Moghadam-Kia, Siamak	<b>ICW-C9-5</b>	Motojima, Yasuhito	P2-014
Mok, My	ICW-B9-6	Motoki, Emi	W45-6
Mokuda, Sho	<b>ICW-B2-2</b> , W27-2	Motomiya, Makoto	S12-2
Momohara, Shigeki	S12-4, ICW-C4-1, <b>W23-2</b> , W31-1, W31-3, W31-5, W66-6, W67-5, W72-1, W75-3, <b>LS9-1</b> , P2-005, P3-050, P3-053, P3-055	Motomura, Hiraku	EL18, W10-4, <b>W36-3</b> , ES6-2, ES12-2, P3-106, P3-132
Momoki, Noriya	W43-1, P1-211, P2-112	Mpofu, Shephard	ICW-C9-6
Momoyama, Gen	P2-043	Mukae, Hiroshi	<b>EL23</b>
Moran, Caroline	ICW-C6-3	Mukai, Akihiko	<b>P2-258</b> , P3-251
Mori, Chimako	W25-3	Mukai, Masaya	P2-243
Mori, Hiroaki	<b>W46-4</b> , P2-008, P3-002	Mukai, Satomi	P3-183
Mori, Ichiro	W35-3, P1-191	Mukai, Tomoyuki	<b>ICW-B1-1</b> , <b>ICW-B4-1</b> , W18-4, <b>P1-023</b> , P2-261
Mori, Masaaki	W6-4, W69-2, <b>W69-3</b>	Mukofujiwara, Yuka	P1-128
Mori, Shigeshi	<b>P3-100</b>	Munakata, Yasuhiko	P3-040, P3-048
Mori, Shunsuke	<b>P3-070</b>	Muneta, Takeshi	<b>S3-3</b>
Mori, Toshihito	W10-1, W71-4	Murai, Yukari	P1-252, P3-005, P3-072
Mori, Yoshiyuki	P2-057, P2-244	Murakami, Daisuke	W68-6, P1-191, <b>P3-243</b>
Morikawa, Jun	<b>P3-254</b>	Murakami, Kanako	<b>W25-3</b>
Morimoto, Chikao	W79-5	Murakami, Ken	ICW-C3-4, ICW-B1-6, W24-2, W27-5, W40-1, W60-5, P1-236, P2-237, P3-067, P3-153, P3-185
Morimoto, Ippei	P2-018	Murakami, Kosaku	W56-2, W63-6, W65-1
Morimoto, Madoka	ICW-C4-6, P1-226, P2-172, P2-174, P2-228	Murakami, Masaaki	W20-2
Morimoto, Shinji	W17-6, P1-233, <b>P2-149</b> , P3-161, P3-201, P3-226	Murakami, Miho	W14-5, P2-036
Morinobu, Akio	ICW-B7-2, W13-6, W17-5, W34-1, <b>P1-008</b> , P2-143, P2-160, P3-068, P3-208	Murakami, Sara	ICW-C4-6, P1-226, <b>P2-172</b> , <b>P2-174</b> , P2-228
Morishima, Atsuyoshi	P1-193, <b>P1-255</b>	Murakami, Teshin	W17-4
Morishima, Yosuke	W15-4	Murakami, Yoshihiko	<b>P2-182</b>
Morishita, Michiko	ICW-C8-2, ICW-C8-3, W4-5, W48-4, P2-199, <b>P3-064</b>	Murakawa, Miyuki	MTE8
Morita, Hiromi	W83-5, P1-085, P1-120, P2-090, P2-094, P2-096, P3-082	Murakawa, Yohko	W18-1, <b>GES-3</b> , P1-188, P2-146, P3-202
Morita, Hiroyuki	W35-3	Muraki, Minoru	P2-230
Morita, Kaoru	S16-4, ICW-B3-6, <b>ICW-B7-3</b> , ICW-B8-3, W17-2, W79-6	Muramatsu, Mizuho	<b>P3-063</b>
Morita, Mitsuhiro	S3-2	Muraoka, Sei	W28-6, W42-1, W59-2, W76-6, P1-104, P1-146, P2-033, P2-034
Morita, Rimpei	ICW-B5-7, W13-5, W62-2, W62-3	Murasawa, Akira	W12-1, W15-5, W23-5, W39-1, W45-4, W52-1, W52-3, W71-1, W74-1, P2-102
Morita, Rinpei	ICW-B3-1	Murashima, Atsuko	GES-3, P2-019, P2-106
Morita, Takayoshi	P2-057, P2-244	Murata, Miho	IS2-5
Morita, Yoshinori	W75-6	Murata, Miki	W81-4, P1-048, P1-098, P3-123
		Murata, Norikazu	<b>P2-041</b> , P3-042, P3-044, P3-045,

	P3-052, P3-054	Nagashima, Takao	W3-1, W59-4
Murata, Okinori	W9-5, P1-124, <b>P2-153</b> , P2-169	Nagata, Masayoshi	P1-052
Murata, Takuji	W26-4, P3-216	Nagatani, Katsuya	W42-2, W59-4, <b>P1-054</b> , P1-199, P2-236, P3-198
Murata, Yosuke	W27-2		
Murata, Yousuke	P2-105, P3-034	Nagatomo, Yasuhiro	W54-5, P1-078, P1-156
Murayama, Go	P1-187, P2-047, <b>P2-249</b>	Nagaya, Yuko	P1-128
Murayama, Takashi	W36-3, P2-028	Nagayama, Yoshio	W52-2, <b>W52-6</b> , P2-079
Murayama, Tomoo	P1-200, P2-187	Nagoya, Satoshi	W33-3, W61-1, W61-2
Muro, Hideki	P2-084, P3-136	Naishiro, Yasuyoshi	W33-3
Muro, Yoshinao	<b>W51-3</b> , P3-167	Naito, Masatoshi	P3-270
Murosaki, Takamasa	<b>W42-2</b> , W59-4, P1-054, P1-199, P2-236	Naka, Ikuko	W34-1, P2-160, P3-208
		Naka, Tetsuji	W11-2
Murota, Atsuko	<b>W13-5</b> , W62-2	Nakabayashi, Akihiko	ICW-C4-6, <b>P1-226</b> , P2-174, P2-228
Muta, Ai	W70-2, <b>W70-3</b> , W78-5, P1-186, P1-202	Nakabayashi, Amane	ICW-C3-4, W24-2, W40-1, W60-5, P1-236, P2-237, P3-067, <b>P3-153</b> , P3-185
Mutoh, Tomoyuki	<b>W27-2</b> , P2-105, P3-034		
<b>N</b>			
Nagabuchi, Yasuo	W66-1, W83-1, P2-042	Nakachi, Shinichiro	S16-4, ICW-B3-4, ICW-B3-6, <b>ICW-B7-4</b> , ICW-B9-3, W66-1
Nagafuchi, Hiroko	P2-058		
Nagafuchi, Yasuo	<b>ICW-B3-4</b> , ICW-B7-4, ICW-B9-3	Nakagawa, Ikuma	ICW-C2-6, W11-4
Nagahara, Hidetake	ICW-C3-4, ICW-B1-6, ICW-B7-5, W24-2, W27-5, <b>W40-1</b> , P3-185	Nakagawa, Jin	W17-1, W17-4, W20-4, W64-5, P1-210
Nagai, Kohei	P1-198	Nakagawa, Koichi	W73-5, P1-111, P2-078
Nagai, Koji	P2-123, P2-189, <b>P3-171</b> , P3-242	Nakagawa, Natsuko	W18-2, W45-6, GES-3, P1-048, <b>P1-098</b> , P2-128, <b>P3-123</b>
Nagai, Takashi	W75-1		
Nagai, Taku	P1-053	Nakagawa, Norio	<b>P2-188</b> , P3-126
Nagai, Tatsuo	W22-2, W48-3, W64-1, W65-2, W78-1, W80-1, P1-157, <b>P2-037</b> , P2-074, P2-101	Nakagawa, Takayuki	<b>S18-2</b>
		Nakagomi, Daiki	W24-1
Nagai, Yoshiki	W13-1, W42-3, W46-3, <b>P1-216</b> , P2-006, P2-260, P3-233	Nakahara, Hideko	W56-2, W82-5, P3-042, P3-044, P3-045, P3-052, P3-054
Nagamine, Ryuji	P2-035, <b>P2-132</b>	Nakahara, Ryuichi	W39-5, W71-2, P1-129, <b>P1-264</b> , P2-270
Nagamine, Satomi	<b>P2-131</b>		
Nagamoto, Takumi	ICW-C5-2, <b>W3-5</b> , W8-2, W15-6, P1-176, P1-225, P1-265, P2-226	Nakahashi, Sumie	ICW-C2-3, ICW-C2-4, ICW-C5-4, ICW-C7-2, P3-004
Nagamura, Norihiro	<b>P1-192</b>	Nakai, Ayako	<b>P1-007</b>
Nagano, Shuji	W7-1, W11-1, W51-2, W73-4, <b>P1-065</b> , P3-033	Nakajima, Akio	ICW-C8-4, P1-208, P2-225
		Nakajima, Arata	<b>W73-5</b> , <b>P1-111</b>
Nagano, Tomoko	P3-270	Nakajima, Ayako	<b>MTE4</b> , W31-1, W31-3, W31-5, W66-6, W67-5, GES-3, <b>LS6-2</b> , P2-005, P3-050
Naganuma, Yasushi	ICW-C1-1, <b>W10-6</b> , W53-6, W81-1, P1-094, P1-141, P3-089		
		Nakajima, Hiroshi	W24-1, W24-6, W50-4
Nagao, Kana	MTE8	Nakajima, Kyoichi	<b>P2-239</b>
Nagaoka, Akiko	P1-110, P2-133	Nakajima, Shihoko	P1-015, P1-016, <b>P1-017</b>
Nagaoka, Shohei	W32-5, W35-2, W37-5, W64-1, W67-3, P1-049, P1-074, P2-059, P3-211	Nakajima, Toshihiro	P1-003
		Nakamachi, Yuji	<b>W40-3</b> , P3-068
Nagare, Yasuaki	W21-2, W30-1, W59-5, P1-240, P2-031, <b>P2-142</b> , P3-152	Nakamura, Akihiko	P2-052, P3-047
		Nakamura, Akinori	W9-1
Nagasaka, Kenji	W29-2	Nakamura, Fumihisa	P2-078
Nagasawa, Eiji	P2-179, P2-197, P3-188	Nakamura, Hideki	<b>S6-3</b> , S6-6, <b>EL17</b> , ICW-C8-1, W22-6, W33-1, W34-4, W37-6, W41-5, <b>W62-4</b> , W64-6, P1-061, P1-160, P2-045, P2-048, P2-205, P3-094, P3-238
Nagasawa, Hayato	P1-033		
Nagasawa, Junya	<b>P2-062</b> , P3-060	Nakamura, Hiroaki	W7-4, W30-3, W32-3, W37-1, W38-2, W54-1, W58-2, W58-3, W83-3, P1-096, P2-063, P2-114, P3-014
Nagasawa, Kohei	W21-3		
Nagasawa, Yosuke	ICW-C4-4, ICW-C9-4, W12-2, W34-6, <b>P1-022</b> , P2-171, P2-203	Nakamura, Hiroshi	W55-4, P1-011, P1-119, <b>P1-137</b> , P3-065
Nagase, Yuichi	W2-1, <b>W52-4</b> , P2-043, P2-138		
Nagashima, Shoichi	P2-043		

Nakamura, Ichiro	W2-1, W82-4, <b>P1-145</b>		P2-060, P2-212, P3-075, P3-092,
Nakamura, Jun	W59-4		P3-093, P3-236
Nakamura, Junichi	P2-136, <b>P3-023</b>	Nakata, Chiai	P1-200, <b>P2-187</b>
Nakamura, Kyohei	W65-5, P1-243	Nakata, Hitoshi	P2-263
Nakamura, Masanori	W18-3, P1-028	Nakata, Jun	P1-255
Nakamura, Masataka	W3-2, <b>W50-3</b> , W77-6, P2-111, P2-216, P3-070, P3-173, P3-176, P3-178	Nakatani, Kimihiko	P3-079
		Nakatani, Teruyuki	<b>P1-079</b>
Nakamura, Mitsuyuki	P3-103	Nakatsue, Takeshi	ICW-C6-4, W2-6, <b>W4-4</b> , W6-6, W41-1, W44-1, W57-6, W65-4, W79-1
Nakamura, Satoru	W7-6, <b>P3-016</b> , P3-126		P2-264
Nakamura, Seiji	S6-1, W62-1	Nakatsuka, Keisuke	P2-264
Nakamura, Shinichiro	<b>W53-1</b>	Nakaya, Hiroyuki	W82-1, <b>P1-229</b>
Nakamura, Tadashi	<b>W61-5</b> , P1-053, P2-059, <b>P3-056</b> , P3-170	Nakaya, Izaya	P3-177
		Nakayama, Akiyoshi	<b>ICW-B2-6</b>
Nakamura, Takashi	W39-2, W63-4, P1-041	Nakayama, Ayano	<b>ICW-C6-2</b>
Nakamura, Takeshi	P2-103, P2-104, P2-116	Nakayama, Masanori	<b>P1-258</b>
Nakamura, Takuji	ICW-C8-4, P1-208, <b>P2-225</b>	Nakayama, Shuichi	W33-2, P3-199, P3-213
Nakamura, Tomoko	W56-1	Nakayama, Takahiro	P3-191
Nakamura, Yoshihide	P3-019	Nakayama, Tsuyoshi	W17-1, W17-4, W20-4, W64-5, P1-210
Nakamura, Yukio	<b>P3-145</b>		<b>S16-3</b> , ICW-C1-6, ICW-C3-5, ICW-C9-2, ICW-C9-3, ICW-B1-3, ICW-B6-2, ICW-B6-6, ICW-B7-7, ICW-B8-1, ICW-B9-1, W14-3, W37-4, <b>W38-6</b> , W41-2, <b>W43-3</b> , W49-6, W55-1, W70-4, W77-2, P1-005, P1-086, P3-015, P3-038
Nakamura, Yuri	ICW-C5-2, W3-5, W8-2, W15-6, P1-176, <b>P1-225</b> , P1-265, P2-226 W46-2, W57-2, P3-234	Nakayamada, Shingo	W36-3, <b>P2-028</b>
			W25-1, W25-2
Nakanishi, Miho	P3-042, P3-044, P3-052, P3-054	Nakazaki, Satoshi	P1-170, P1-231, P3-068, P3-155
Nakanishi, Tae	<b>W6-1</b> , W19-2, W24-5	Nakazawa, Daigo	P1-179, <b>P2-003</b> , P3-083
Nakanishi, Takashi	MTE8	Nakazawa, Takashi	W12-1, W15-5, W23-5, W39-1, <b>W45-4</b> , W52-1, W52-3, W71-1, W74-1, P2-102
Nakano, Haruki	P1-068, P1-102	Nakazawa, Takuya	P1-187, P2-249
Nakano, Hiromasa	<b>P2-235</b>	Nakazono, Kiyoshi	W56-1
Nakano, Hiroto	ICW-C1-6, ICW-C3-5, ICW-C9-2, ICW-C9-3, ICW-B6-2, ICW-B6-6, <b>ICW-B7-7</b> , ICW-B8-1, ICW-B9-1, W14-3, W37-4, W38-6, W41-2, W43-3, W49-6, W55-1, W70-4, W77-2, P1-005, P1-086, P3-015		W75-1
Nakano, Kazuhisa	W57-4, P1-121, P1-247	Nakazaki, Satoshi	<b>W52-2</b> , W52-6, P2-079
		Nakazawa, Daigo	<b>W23-6</b> , <b>W54-6</b> , P3-115, P3-225
Nakano, Kenji	ICW-C6-4, W4-4, W6-6, W41-1, W44-1, W57-6, <b>W65-4</b> , W79-1	Nakazawa, Takashi	W58-4, <b>W69-1</b> , P2-215, P3-146
Nakano, Masaaki	W17-1, <b>W17-4</b> , W20-4, W64-5, P1-210	Nakazawa, Takuya	SW1-3, W6-2, W68-4, P1-018, P1-066, P2-213, P2-218, P2-221
		Nakazono, Kiyoshi	ICW-C7-4, ICW-C8-2, ICW-C8-3, W48-4, P2-199, P3-064
Nakano, Shota	<b>P3-141</b>		ICW-B4-2, W11-2, P1-255
Nakano, Shunji	W3-3, P1-093, <b>P2-022</b> , P3-028, P3-043	Narazaki, Mariko	<b>ICW-B1-3</b>
Nakano, Souichiro	W75-6	Narazaki, Masashi	ICW-C2-5, <b>LS23-1</b> , P1-031, P2-085, P2-100, P3-260
		Narisawa, Manabu	<b>P1-134</b> , P1-141
Nakano, Taiji	W26-1, W26-5	Narita, Akihiro	ICW-C6-4, W4-4, W6-6, W12-1, W15-5, W23-5, W33-5, W41-1, W44-1, W57-6, W65-4, W79-1, P2-102
Nakaseko, Haruna	<b>W13-3</b> , W33-4, P3-181, P3-250		P3-040, P3-048
Nakashima, Akikatsu	W11-1, W33-5, P3-270	Narita, Atsushi	W11-3, W39-5, W45-1, W56-5, W73-3, <b>P3-117</b>
Nakashima, Hitoshi	ICW-C1-2, W6-3, W22-6, W67-6	Narita, Ichie	W11-3, W45-1, W56-5, <b>W73-3</b> , P3-117
Nakashima, Munetoshi	W50-1, W51-3, W63-6		
Nakashima, Ran	P1-247	Narushima, Katsuhiko	
Nakashima, Satoru	W9-4, <b>W28-4</b> , W33-6, W34-3, W61-6, W65-6, P1-009, P1-237, P3-222	Nasu, Yoshihisa	
Nakashima, Shusaku	P3-121	Natsumeda, Masamitsu	
Nakashima, Yasuharu	ICW-C8-1, W33-1, W34-4, W37-6, W41-5, W62-4, W64-6, P1-061, P1-160, <b>P2-045</b> , P2-048, P2-205, P3-094, P3-238		
Nakashima, Yoshikazu	<b>W38-4</b> , W70-6, <b>W74-2</b> , P1-204,		
Nakashita, Tamao			

Natsumoto, Bunki	<b>ICW-C5-6</b> , W22-4, W28-1		P1-152, P1-171, P2-166, P2-173,
Nawata, Aya	W43-3		P2-175, P3-116, P3-204
Nawata, Yasushi	P1-220	Nishioka, Hiroaki	W63-3, P2-208
Nemoto, Takuya	P2-025, P2-047	Nishioka, Junko	W19-2
Nerome, Yasuhito	W26-3, W26-6	Nishioka, Kusuki	P1-003, P1-180, P3-069
Netsu, Takahiro	ICW-B7-6, W2-6, <b>W52-5</b> , P1-045	Nishioka, Yasuhiko	P2-255, P2-257
Nibu, Kimio	P1-119	Nishioka, Yosuke	P3-040, P3-048, P3-069
Nii, Takuro	W16-5, <b>W31-2</b> , W32-1, W54-2, P1-127, P2-024, P2-241	Nishioka, Yuichi	W19-2, P2-052, P3-047
Niimi, Akio	W23-6, W54-6, P3-115, P3-225	Nishisato, Takuji	P3-066
Niuro, Hiroaki	<b>S8-2</b> , <b>W11-1</b> , W17-1, W17-4, W20-4, W47-1, W47-2, W50-6, W62-5, W64-5, P1-210, P2-202	Nishiura, Etsuko	<b>P2-266</b>
Niitsu, Mamoru	<b>EL10</b>	Nishiura, Satoko	P2-268
Niki, Yasuo	ICW-B3-1, W63-2, W83-6	Nishiwaki, Atsuma	ICW-C4-4, ICW-C9-4, W12-2, <b>W34-6</b> , P2-171, P2-203, P3-024
Nin, Kazuko	W59-3, W82-3	Nishiyama, Susumu	<b>S6-5</b> , W5-2, W33-2, <b>W41-3</b> , P1-232, P1-234
Ninomiya, Yukari	P1-124, P2-153, P2-169	Nishizaka, Hiroaki	W11-1
Nishi, Eiko	W54-5, <b>P1-072</b> , P1-078, P2-121, P3-090	Nishizawa, Tetsuro	P2-223
Nishi, Hideto	P1-259, P3-263	Nishizawa, Tohru	W68-5, W82-2, P1-246, P3-186, P3-214
Nishida, Keiichiro	S10-3, <b>MTE12</b> , ICW-B4-1, W11-3, W39-5, W45-1, W56-5, W63-2, W71-2, W73-3, W83-6, <b>LS20-1</b> , P1-023, P1-129, P1-264, P2-137, P2-270, P3-117	Nobata, Hironobu	W66-5, <b>P2-039</b>
Nishida, Miwa	ICW-B7-2, W13-6, W17-5, W34-1, P3-208	Nobuhara, Yumiko	<b>P1-170</b> , P1-231, P3-155
Nishide, Masayuki	W11-2	Noda, Kentaro	<b>W6-5</b> , W49-5, P1-021, P2-113
Nishikawa, Ayumi	S6-2, <b>W62-2</b>	Nogi, Shinichi	W16-3, W51-4, P1-112, P1-181, <b>P2-176</b> , P3-158, P3-175
Nishikawa, Keiko	W64-3, P2-012, <b>P2-013</b>	Noguchi, Atsushi	ICW-C2-6, ICW-B4-7, <b>W11-4</b>
Nishikawa, Masataka	W56-1, P1-135, P2-079, P2-122	Noguchi, Ikuyo	<b>P1-267</b>
Nishikawa, Takuji	W2-1, W52-4, <b>P2-043</b> , P2-138	Noguchi, Takaaki	ICW-C6-6, ICW-C6-7, <b>W57-5</b>
Nishikomori, Ryuta	<b>EL6</b> , W9-3, W9-4, P1-254	Noguchi, Yoriko	W40-3
Nishimi, Airi	W60-4, GES-2, P2-148, P3-086	Nojima, Shigeru	P1-228
Nishimi, Shinichiro	<b>W60-4</b> , P2-148, P3-086	Nojima, Takaki	W14-6, P1-185, <b>P1-230</b> , P2-052, P2-170, P3-047, <b>P3-125</b>
Nishimoto, Norihiro	W14-5, P2-012, P2-036	Nojima, Yoshihisa	W5-4, W29-3, W79-2
Nishimura, Akito	<b>P2-089</b> , <b>P2-093</b>	Nojiri, Sho	P2-134
Nishimura, Hiroyuki	W64-3, P2-012, P2-013	Nomoto, So	P1-113, P2-127
Nishimura, Keisuke	ICW-B7-2, W13-6, <b>W17-5</b> , W34-1, P1-008, P3-208	Nomura, Atsushi	P1-252, <b>P3-005</b> , P3-072
Nishimura, Keita	W2-1	Nomura, Shigeru	W9-3
Nishimura, Ken-ichi	W69-3	Nomura, Shosaku	W68-5, W82-2, P1-246, P3-186, P3-214
Nishimura, Koji	P1-033, P1-082, <b>P2-194</b>	Nomura, Yoshihisa	<b>W43-1</b> , P1-211, P2-112
Nishimura, Naoya	<b>P2-151</b>	Nonaka, Fumiaki	W9-6, W22-3, P3-224
Nishimura, Shinsuke	W43-1	Nonaka, Yukiko	W26-2, W26-3, W26-6
Nishina, Hirokazu	W77-5, <b>P1-155</b>	Nosyo, Tomoko	W81-4
Nishina, Naoshi	ICW-C5-5, P3-207	Noto, Daisuke	IS2-5
Nishino, Akira	<b>W35-1</b> , P3-107	Nozaki, Masahiro	P1-128
Nishino, Ayako	ICW-C8-1, <b>W7-1</b> , W33-1, W34-4, W37-6, W41-5, W64-6, P1-061, P1-160, P2-045, P2-048, P2-205, P3-094, P3-238	Nozaki, Takamasa	ICW-C4-4, ICW-C9-4, W12-2, W34-6, P1-022, <b>P2-171</b> , P2-203
Nishino, Jinju	W2-1, W29-4, <b>W29-5</b> , <b>W54-4</b> , W70-5, W71-4, W81-5, W82-1, W83-2, W83-4, P2-007, P2-008, P2-009, P2-055, P3-129	Nozaki, Yuji	W21-2, <b>W30-1</b> , W56-2, W59-5, P1-240, P2-031, P2-142, P3-152
Nishino, Jo	W44-2, P1-178, P3-080, P3-183	Nozawa, Kazuhisa	P1-162, P1-163, P2-047
Nishioka, Aki	S6-4, W12-6, W41-6, <b>W48-1</b> , W56-3,	Nozawa, Tomo	W69-3
		Nozawa, Youhei	P1-068, <b>P2-163</b>
		Nozawa, Yukiko	W4-4, <b>W41-1</b> , W44-1, W57-6, W79-1
		Nuka, Hiromi	W4-2, W44-6, W60-3, P1-209, P1-242, P2-120, <b>P3-192</b>
		Nuka, Satoshi	P3-077
		Nunokawa, Takahiro	W13-1, W42-3, W46-3, P1-076, P1-216, P2-006, P2-260, P3-233

<b>O</b>			
Obata, Jyunichi	P3-007	Ohashi, Keiji	ICW-C8-2, ICW-C8-3, <b>W4-5</b> , W48-4, P1-232, P2-199, P3-064
Obi, Maiko	W48-6, P2-195, <b>P2-204</b> , P3-150, P3-193	Ohashi, Satoru	<b>W10-1</b> , W71-4, W76-1
Ochi, Kensuke	S12-1, P2-036	Ohira, Hiromasa	P2-185, P2-211, P3-030, P3-184
Ochi, Takahiro	P2-036	Ohishi, Masanobu	<b>P3-121</b>
Oda, Aya	W18-6	Ohishi, Ryuta	P1-141
Oda, Hiromi	W8-4, W13-4	Ohjimi, Hisae	W28-2, <b>W43-4</b> , P2-182
Oda, Katsuhiko	W4-1, P2-018, <b>P3-194</b>	Ohmura, Kazumasa	ICW-C2-6, W11-4
Oda, Kazuhiro	P1-107, <b>P2-117</b>	Ohmura, Koichiro	<b>S11-3</b> , W41-6, W48-1, W50-1, W56-2, W63-6, W65-1
Oda, Keiko	P3-248	Ohnishi, Ako	P2-262
Oda, Kosaku	<b>P1-105</b> , P1-267, <b>P2-082</b>	Ohnishi, Hideo	P2-014
Oda, Ryo	ICW-B1-6, ICW-B7-5, W7-6, W19-4, W27-5, W40-1, W45-3, W60-5, <b>W72-4</b> , P2-224, P3-016, P3-126, P3-185	Ohnishi, Isao	W75-5
Oda, Yuji	MTE8	Ohnishi, Yasuko	MTE8
Odani, Toshio	W47-5, P2-233	Ohno, Hiroshi	MTE8
Oddis, Chester V.	ICW-C9-5	Ohno, Shigeru	<b>S10-6</b> , <b>MTE1</b> , W32-5, W64-1, P2-086
Ode, Kazu	<b>W33-2</b> , P1-169, P1-196, P2-196, P3-199, P3-213	Ohnuma, Kei	W79-5
Oga, Kenya	W45-2	Ohnuma, Kenichiro	W40-3
Ogasawara, Michihiro	W34-2, W55-2, W73-2, <b>LS23-2</b> , P1-016, P1-017, P2-025, P2-047	Ohsawa, Yoshikiyo	P2-263
Ogasawara, Takashi	W68-3, <b>P3-085</b>	Ohshima, Shiro	ICW-C4-6, W16-5, W29-6, W31-2, W32-1, <b>W54-2</b> , P1-127, P2-024, P2-241
Ogata, Atsushi	ICW-B4-2, W11-2, P1-255	Ohta, Akihideo	W3-4, W21-3, W37-2, W66-4, P1-087, P1-108, P1-190, P2-168, P2-214, P3-008
Ogata, Koji	W33-2, P1-169, <b>P1-196</b> , P2-196, P3-199, P3-213	Ohta, Yasuhiro	W38-3
Ogata, Shohei	W22-5	Ohtani, Masafumi	P1-035
Ogawa, Eisuke	W22-2, W48-3, W65-2, W78-1, P1-157, <b>P2-074</b>	Ohtsubo, Hideo	W7-1, W56-4, W57-4, <b>P1-053</b> , <b>P1-121</b> , P1-247
Ogawa, Kunikazu	W42-5, W46-6	Ohtsuji, Mareki	W64-3, <b>P2-012</b>
Ogawa, Megumi	<b>W22-4</b>	Oi, Katsuhiko	P1-070, <b>P2-077</b> , P2-164
Ogawa, Noriyoshi	S1-1, <b>ICW-C3-2</b> , W38-3, P1-254	Oikawa, Noboru	W10-5
Ogawa, Yoshikazu	<b>W12-4</b> , P3-012	Oikawa, Yuka	<b>P1-124</b> , P2-153, P2-169
Ogawa, Yoshimasa	W23-2, P3-076	Oishi, Makoto	<b>P2-205</b>
Ogihara, Hideki	P1-183, P1-241, P2-247, P3-018, P3-112, P3-247	Oka, Hiroshi	W35-5, P1-207, <b>P3-103</b>
Ogihara, Yoshihito	<b>W22-5</b>	Oka, Hiroyuki	W29-5, W54-4, W76-1
Ogino, Hiroko	W30-5, W31-6, W39-4, W63-5, <b>W72-3</b> , P3-036	Oka, Shomi	P2-056, <b>P2-059</b>
Ogino, Masaaki	W83-5, P1-085, P1-120, P2-090, P2-094, P2-096, P3-082	Oka, Yumiko	P3-174
Ogishima, Hiroshi	S6-6, W13-2, W28-3, W49-2, W49-3, W55-3, P1-030, <b>P1-032</b>	Okabe, Koya	<b>P3-178</b>
Ogita, Chie	W12-6, W41-6, W43-2, W56-3, P2-166, P2-173, P2-175, P3-116	Okada, Akitomo	ICW-C1-2, W7-1, P2-045, P2-048
Oguchi, Takeshi	W12-5, W36-2, W36-4, W38-5, P1-114, P2-125	Okada, Harutsugu	W55-5, <b>P1-083</b> , P3-109, P3-113, P3-266
Oguchi, Yoko	W6-2	Okada, Hideyuki	<b>P3-229</b>
Oguma, Asako	W47-4, P1-126, P1-213	Okada, Masato	S5-4, <b>SW1-1</b> , P2-229, P3-003, P3-040, P3-048, P3-220, P3-261
Ogura, Takehisa	ICW-C2-3, ICW-C2-4, ICW-C5-4, <b>ICW-C7-2</b> , P3-004	Okada, Moe	P2-102
Oguro, Nao	GES-2, P1-028, <b>P1-235</b> , P1-239, P2-023, P2-148, P3-086	Okada, Rika	P1-151, <b>P1-206</b> , P1-223, P2-246
Oh, Koei	W18-3, W75-1	Okada, Takashi	<b>P3-196</b>
Ohara, Yuri	P2-229, P3-003, P3-220	Okada, Yosuke	ICW-B1-3
Ohashi, Hiroyuki	ICW-C3-2, W38-3, P1-254	Okada, Yukinori	<b>S9-4</b> , <b>ICW-B2-7</b>
		Okamoto, Akiko	SW1-3, <b>W6-2</b> , W8-1, W64-1, W68-4, P1-018, P2-213, P2-218, P2-221
		Okamoto, Akira	<b>W5-1</b> , W5-2, W56-1, W64-1
		Okamoto, Junichi	ICW-C1-1, <b>W53-6</b> , P3-089
		Okamoto, Kensaku	W18-5, P2-184, P2-232
		Okamoto, Masaki	ICW-B3-2, W9-2, P1-175, P2-231
		Okamoto, Nami	W26-4, <b>P3-216</b>
		Okamoto, Tomoko	IS2-5

Okamoto, Yasuyoshi	P3-110	Omura, Shin-ichiro	<b>ICW-C5-1, W49-1, P3-096</b>
Okamoto, Yuko	W48-2, W64-2, W65-3, W77-5, P1-154, P1-155, P1-167, P1-219, P2-150, P2-198, P2-217, P3-107	Omura, Yuichi	P2-162
Okamura, Eri	<b>P3-190</b>	Onbe, Tsuneto	W43-1, P2-112
Okamura, Koichi	ICW-C2-7, <b>ICW-C3-6</b> , W30-4, P1-042, P1-136, <b>P1-268</b> , P3-013, P3-133	Onda, Akiko	P1-018
Okamura, Tomohisa	S16-4, <b>ICW-B3-6</b> , ICW-B7-3, ICW-B7-4, ICW-B8-3, ICW-B9-3, W17-2, W79-6	Onishi, Akira	W17-5, W34-1, P2-143, P2-160, P3-208
Okamura, Yuki	W17-3	Onishi, Ikuko	<b>P2-032</b>
Okano, Tadashi	<b>W7-4</b> , W30-3, <b>W32-3</b> , W37-1, W38-2, W54-1, W58-2, W58-3, W81-3, W83-3, P1-096, P2-016, P2-063, P2-114, P3-014	Onishi, Kae	W13-1, W42-3, W46-3, P1-216, P2-006, <b>P2-260</b> , P3-233
Okano, Takaichi	W13-6, W17-5, W34-1, P2-143, P3-208	Onishi, Makoto	W27-2, P2-105, P2-262, P3-034, P3-256
Okano, Yutaka	P1-029, P2-165, P2-250	Onishi, Sachiko	<b>W51-6</b> , P2-252, P3-180
Okayama, Akihiko	ICW-B6-3, W54-5, P1-078, P1-156, P2-234	Onishi, Takahiro	<b>P1-180</b>
Okayama, Yoshimichi	W17-3	Onishi, Yasutaka	W5-1
Okazaki, Hideki	P2-012	Ono, Kumiko	W29-5, W54-4, <b>W76-1</b>
Okazaki, Ken	P3-121	Ono, Masanori	<b>P2-269</b>
Okazaki, Masaki	P2-197	Ono, Nobuyuki	W3-4, W37-2, W66-4, P1-087, P1-108, P1-190, P2-168, P2-214, <b>P3-008</b>
Okazaki, Mizue	ICW-C5-3, P2-157	Ono, Yukihide	<b>W3-4</b> , W37-2, W66-4, P1-087, P1-108, P1-190, P2-168, P2-214, P3-008
Okazaki, Ryota	ICW-B3-5, W78-3, <b>P2-190</b>	Onoda, Satoru	W44-2, P1-178, P3-080, P3-183
Okazaki, Shunichiro	W33-3, <b>W61-1, W61-2</b>	Onuma, Kenji	<b>P3-130</b>
Okazaki, Takahiro	W28-2, W43-4, P1-177, P2-058, P2-182	Ooka, Seido	W28-2, W43-4, P1-177, P1-198, P2-058, P2-163, P2-182
Oki, Hiroharu	ICW-C1-1, W10-6, W81-1, <b>P1-094</b> , P1-141, P3-089	Oonari, Shinpei	P1-220
Oku, Kenji	ICW-C2-6, W11-4	Oorui, Hiroshi	W53-6, W81-1, P1-094, P1-134
Okubo, Hiroshi	P1-131, <b>P1-132</b>	Oribe, Motohiro	<b>W36-5</b> , P2-052, <b>P2-075</b> , P3-047
Okubo, Mai	SW1-3, W6-2, W68-4, <b>P2-213</b> , P2-218, P2-221	Origuchi, Tomoki	ICW-C8-1, <b>W22-6</b> , W33-1, W34-4, W37-6, W41-5, W64-6, P1-061, P1-148, P1-160, P2-045, P2-048, P2-205, P3-094, P3-238
Okubo, Naoaki	<b>P1-086</b>	Ormsby, Renee T.	ICW-C6-3
Okuda, Kosuke	<b>P1-131</b> , P1-132, P2-103, P2-104, P2-116	Orui, Hiroshi	ICW-C1-1
Okuda, Sayuri	<b>W68-1</b> , W78-2	Oryoji, Daisuke	W17-1, W17-4, W50-6, W64-5
Okuda, Shota	P1-141	Oryoji, Kensuke	W11-1, W73-4, P2-098, <b>P2-115</b> , P2-147, P3-035, P3-239
Okuda, Toshiharu	<b>P1-147</b>	Osada, Atsumu	<b>W35-2</b> , W37-5, W67-3, P1-049, <b>P1-074</b> , P3-211
Okuda, Yasuaki	W27-2, W61-3, <b>P2-105</b> , P3-034	Osada, Ryusuke	P3-132
Okuda, Yoshiki	P2-091	Osaki, Yukio	<b>LS27</b>
Okumura, Ko	W79-5	Osawa, Hikota	P1-261, P2-198, <b>P2-259</b>
Okumura, Noriaki	<b>P1-107</b> , P2-117	Osawa, Suguru	P3-044, P3-045, P3-054
Okuno, Hiroshi	ICW-C1-2	Oshida, Midori	P2-269
Okura, Chisa	ICW-C2-7, ICW-C3-6, W30-4, <b>P1-042</b> , P1-136, P3-013, <b>P3-133</b>	Oshikawa, Hideto	W30-2, W37-3, P2-201, P3-009
Okura, Toshiaki	P2-119	Oshima, Hisaji	<b>MTE16</b> , ICW-C5-4, W28-5, W42-5, W46-6, W76-4, W76-5, P2-140, P3-206, P3-210
Okuyama, Ayumi	ICW-C7-3, W16-1, W76-3, P1-033, <b>P1-062</b> , P1-115, P3-262	Oshima, Kahori	P2-179, <b>P3-188</b>
Omae, Takanori	P2-136	Oshima, Miho	<b>W75-5</b> , W83-1, P2-042
Omata, Yasunori	W29-5, W54-4, W76-1, P2-055, <b>P3-129</b>	Osone, Yasuo	P1-029, P2-165, P2-250
Omoteyama, Kazuki	<b>P1-010</b> , P1-011, P1-012, P2-163	Ota, Keisuke	P2-108
Omoto, Atsushi	W6-3, W66-3, W67-6, <b>P1-161</b> , <b>P2-110</b> , P3-187	Ota, Masanari	W40-6, P1-142, P3-131, P3-134, <b>P3-140</b>
		Ota, Miho	S6-1
		Ota, Mineto	W22-4, W28-1, <b>W66-1</b>
		Ota, Muneo	P3-160

Ota, Shun-ichiro	W17-1, W17-4, W20-4, W50-6, <b>W64-5</b> , P1-210	<b>Q</b> _____	
Ota, Shusuke	<b>P3-110</b>	Qian, Wang	ICW-C9-1
Ota, Toshiyuki	W21-3, <b>W51-2</b> , W73-4, P1-065, P3-033	<b>R</b> _____	
Ota, Yasuhiro	ICW-C3-2	Reeves, Westley H.	P2-021
Ota, Yuichiro	W3-6, <b>W44-4</b>	Ri, Shinkai	W21-2, W30-1, W59-5, P1-240, <b>P2-031</b> , P2-142, P3-152
Ota, Yuko	W77-3	Rider, Lisa G	S17-1
Otaki, Yasuhiro	P1-102	Rokutanda, Ryo	<b>P2-229</b> , P3-003, P3-220
Otani, Hiroshi	W12-1, W15-5, W23-5, W45-4, W52-1, W52-3, W71-1, W74-1	Rooney, Terence	W69-4
Otani, Kazuhiro	W6-5, <b>P2-078</b> , <b>P2-113</b>	Ryu, Junnosuke	SW2-6
Oto, Yosuke	W6-5, P2-113	Ryuge, Akihiro	P1-252
Otsu, Makoto	S17-6, <b>EL8</b>	<b>S</b> _____	
Otsuka, Eiji	P2-052, P3-047	Sada, Eiji	P2-252, P3-180
Otsuka, Fumio	P3-230	Sada, Ken-ei	S15-1, <b>S15-4</b> , ICW-C7-4, ICW-C8-2, ICW-C8-3, W4-5, W34-5, W48-4, W69-2, W69-3, W79-4, P1-158, P2-199, P3-064
Otsuka, Kumiko	GES-2, P2-148	Sadanaga, Yuri	W3-4, W37-2, W66-4, P1-087, P1-108, P1-190, <b>P2-168</b> , P2-214, P3-008
Otsuka, Takanobu	P1-128	Sadatsuki, Ryo	S3-1
Otsuka, Takeshi	W11-1	Saegusa, Jun	<b>ICW-B7-2</b> , W13-6, W17-5, W34-1, W40-3, P1-008, P2-143, P3-068, P3-208
Otsuka, Yukimi	<b>P2-202</b>	Saeki, Satoshi	W70-1
Ouchi, Kazutaka	P2-188, <b>P3-126</b>	Saeki, Takako	<b>W33-5</b> , P3-154
Oura, Takashi	P3-255	Saeki, Yukihiko	ICW-C4-6, ICW-B4-2, W16-5, W31-2, W32-1, W45-5, W54-2, P1-127, P2-024, P2-241
Owada, Takayoshi	<b>W55-5</b> , P1-083, P3-109, P3-113, P3-266	Saffar, Bahareh	ICW-B5-3
Owaki, Hajime	W56-1, P1-135, P2-079, P2-122	Sagara, Akihiro	P1-203, P2-156
Oyakawa, Tomo	W12-1, W15-5, W23-5, W45-4, <b>W52-1</b> , W52-3, W71-1, W74-1	Sagawa, Akira	<b>P2-030</b> , P2-050, P2-052, P3-047, <b>P3-048</b>
Oyama, Teruyasu	P2-130	Sagawa, Risa	ICW-C3-4, W24-2, W27-5, W60-5, P1-236, P2-237, P3-067, P3-153, P3-185
Oyama, Tetsu	P2-052, P3-047, P3-125	Sagawa, Tomoya	P3-153
Oyama, Yukako	P1-252, P3-005	Sagisaka, Tamaki	P1-254
Oyama, Yuta	P3-191	Sahara, Akiko	<b>W8-2</b>
Oyamada, Akiko	P3-121	Saiga, Kenta	P1-129
Ozaki, Hiroki	W9-4, W28-4, <b>W33-6</b> , W34-3, W61-6, W65-6, P1-009, P1-237, P3-222	Saio, Yukie	<b>P3-011</b> , <b>P3-104</b>
Ozaki, Ryohiko	P2-257	Sairyo, Koichi	P1-004, P3-141
Ozaki, Shoichi	S15-1, W28-2, W35-6, W43-4, P1-177, P1-198, P2-058, P2-182	Saisho, Koichiro	W83-2, <b>W83-4</b> , P2-007, P2-059, P3-001, P3-021
Ozaki, Takashi	P2-162	Saita, Yoshitomo	S3-1
Ozaki, Takuro	P2-189, <b>P3-240</b>	Saito, Atsushi	W12-6, W41-6, W48-1, W56-3, <b>P1-152</b> , P1-171, P2-166, P2-173, P2-175, P3-116
Ozaki, Toshifumi	S10-3, W39-5, W71-2, P1-129, P1-264, P2-137, P2-270	Saito, Hideki	<b>P2-092</b>
Ozaki, Yoshio	W56-2, W68-5, W75-4, <b>W82-2</b> , P1-246, P2-126, P3-186, P3-214	Saito, Kazuyoshi	<b>S4-1</b> , S6-6, <b>EL1</b> , ICW-C1-6, ICW-C3-5, ICW-C9-2, ICW-C9-3, ICW-B6-2, ICW-B8-1, ICW-B9-1, W37-4, W38-6, W41-2, W43-3, W49-6, W55-1, W68-2, W70-4, W77-2, <b>LS12</b> , <b>ES3-1</b> , P1-086, P3-015, P3-038
Ozaki, Yusuke	P1-025, P3-217, <b>P3-219</b>		
Ozato, Keiko	W64-4		
Ozawa, Ryota	<b>P2-200</b>		
Ozawa, Yuki	W71-6, P1-092		
Ozawa, Yuko	<b>P3-197</b>		
Ozeki, Takaya	<b>P3-151</b>		
Ozeki, Toshikazu	P1-252, P3-005, P3-072		
<b>P</b> _____			
Parousis, Alexa	<b>ICW-B5-2</b>		
Pelletier, Jean-Pierre	ICW-B5-1		
Pile, Kevin D	<b>S13-2</b>		
Pilkington, Clarissa	S17-1		

Saito, Kiwamu	W1-4, W2-2, W12-3, W16-2	Sasajima, Tomomi	<b>P3-177</b>
Saito, Masahiro	W43-3, P2-264	Sasaki, Akiko	ICW-C1-1, W10-6, W53-6, <b>W81-1</b> , P1-094, P1-134, P1-141, P3-089
Saito, Masaki	W25-4		
Saito, Masanobu	S12-3	Sasaki, Kan	ICW-C1-1, W10-6, W53-6, P1-094, P1-141, P3-089
Saito, Mayu	GES-2, P1-239, P2-046, P3-086		
Saito, Rintaro	ICW-C5-2, W3-5, W8-2, W15-6, <b>P1-176</b> , P1-225, P1-265, P2-226	Sasaki, Nobuhito	W9-5, P1-124, P2-153, P2-169
		Sasaki, Noriko	W16-3, W51-4, <b>P1-112</b> , P1-181, P2-176, P3-158, P3-175
Saito, Shu	W10-2, W10-5, W17-3, W53-3, W53-4, W53-5, P2-130, P3-088		
		Sasaki, Oh	W22-4, W66-1, W83-1, P2-042
Saito, Takao	W33-5	Sasaki, Rie	P1-070, P2-077, P2-164
Saito, Tetsuya	W14-4, <b>P1-039</b>	Sasaki, Satoshi	<b>P3-017</b>
Saito, Tomoyuki	W52-3, W71-6, P1-092, P1-110, P2-133	Sasaki, Sho	W16-3, W51-4, P1-112, P1-181, P2-176, P3-158, <b>P3-175</b>
Saitoh, Masakatsu	S14-3, P3-100	Sasaki, Shoichi	<b>P2-191</b>
Saka, Kumiko	W77-5, <b>P1-154</b>	Sasaki, Takeshi	P1-217
Sakaguchi, Shota	W54-5, P1-072, P1-078, P2-121, <b>P3-090</b>	Sasaki, Tamaki	<b>P3-235</b>
		Sasaki, Toshiharu	W68-5, P1-246, P3-186, <b>P3-214</b>
Sakai, Kenji	W21-2, W30-1, W59-5, <b>P1-240</b> , P2-031, P2-142, P3-152	Sasaki, Tsuyoshi	ICW-C2-7
		Sasaki, Yoshiko	W81-2
Sakai, Norihiko	P1-203, P2-156	Sato, Akiko	<b>W55-4</b> , P1-137, P3-065
Sakai, Ryoko	W29-2	Sato, Aya	W25-4
Sakai, Ryota	<b>ICW-C7-3</b> , W16-1, W76-3, P1-033, P1-062, P1-115, P3-262	Sato, Eri	W5-5, W31-3, W31-5, W66-6, P2-005, P3-050
Sakai, Tomoyuki	ICW-C8-4, P1-208, P2-225	Sato, Hiroe	ICW-C6-4, W4-4, W6-6, W41-1, W44-1, <b>W57-6</b> , W65-4, W79-1
Sakai, Yoshitada	W56-1, P1-040		
Sakairi, Toru	W5-4, W29-3	Sato, Hiroko	P1-141, P1-159
Sakamoto, Fumihiko	P1-031, P2-085, P3-260	Sato, Hiroshi	W28-6, W42-1, W59-2, W76-6, P1-104, P1-146, <b>P2-033</b> , P2-034
Sakamoto, Tatsuhiko	P3-105		
Sakashita, Aki	W66-3, P1-161, P2-110, <b>P3-187</b>	Sato, Kazuki	S12-1
Sakata, Kei	ICW-B1-3, ICW-B6-6, ICW-B9-1, W14-3	Sato, Kojiro	ICW-B1-4, W13-4, W60-1, W79-2, P1-173, P1-212, P1-249, P2-118, P3-001
Sakata, Komei	W67-2, P1-153, P1-189, <b>P1-205</b> , P2-141	Sato, Masao	<b>P2-038</b> , P2-265, P3-189, P3-257
Sakata, Ryosuke	P1-259, <b>P3-263</b>	Sato, Michihito	P1-033, <b>P1-082</b> , P2-194
Sakaue, Saori	W22-4, P2-183	Sato, Osamu	P3-077
Sakawa, Akira	W54-1	Sato, Seidai	P2-257
Sako, Keisuke	P1-203	Sato, Shinichi	<b>EL5</b>
Saku, Aiko	<b>W24-6</b>	Sato, Shinji	<b>S17-7</b> , ICW-C9-5, W16-3, <b>W51-4</b> , P1-112, P1-181, P2-176, P3-158, P3-175, P3-233
Sakuma, Michitomo	<b>P2-049</b>		
Sakuma, Yu	<b>W72-1</b>	Sato, Shuzo	<b>P2-185</b> , P2-211, P3-030, P3-184
Sakuma, Yuko	W65-2, <b>W80-1</b> , P2-101	Sato, Takeo	W42-2, P1-054, <b>P1-199</b> , P2-236, P3-198
Sakuraba, Koji	<b>W40-6</b> , P1-142, P3-128, P3-131, P3-134, P3-140		
		Sato, Tomomi	ICW-C8-4, <b>P1-208</b> , P2-225
Sakuraba, Tsutomu	W75-2, W83-5, P1-085, P1-120, P2-090, P2-094, P2-096, <b>P3-029</b> , P3-082	Sato, Tomoo	P1-003
		Sato, Toshiyuki	P1-010, P1-198
Sakurai, Keiichi	ICW-B3-4, ICW-B7-4, ICW-B9-3	Sato, Wakiro	IS2-5
Sakurai, Noriyuki	W5-4, W29-3	Sato, Yurie	<b>ICW-C9-2</b> , ICW-C9-3, W49-6
Sakurai, Takeo	ICW-B3-1	Satoh, Koichiro	<b>P3-031</b>
Sakuta, Takeo	<b>P2-261</b>	Satoh, Minoru	<b>S14-4</b> , ICW-C9-2, ICW-C9-3, W49-6, P2-021
Sano, Hajime	S6-4, W12-6, W21-1, W41-6, W43-2, W48-1, W56-3, P1-152, P1-171, P2-059, P2-166, P2-173, P2-175, P3-042, P3-052, P3-116, P3-204, P3-205	Saura, Ryuichi	<b>MTE8</b>
		Sawa, Naoki	<b>W2-5</b> , W4-6, W21-6, W48-5, W78-6, P2-107
Sano, Hiroshige	<b>P1-045</b>		
Sasahara, Sayuri	<b>P2-265</b> , P3-257	Sawabe, Takuya	W11-1, W47-4, P1-126, P1-213
Sasai, Tsuneo	<b>P2-207</b>	Sawada, Chiharu	P1-253
		Sawada, Jin	P3-044, P3-054
		Sawada, Naoya	W27-2, P2-105, P3-034



Sawada, Tetsuji	W46-4, P2-008	Shida, Haruki	ICW-C2-6, W11-4, W25-1, <b>W25-2</b>
Sawai, Takashi	P1-020	Shidara, Kumi	<b>W31-1</b> , W31-3, W31-5, W66-6, W67-5, P2-005, P3-050
Sawaki, Toshioki	W13-1, W42-3, W46-3, P1-216, P2-260, P3-233	Shiga, Toshihiko	<b>W21-2</b> , W30-1, W59-5, P1-240, P2-031, P2-142, P3-152
Sawamukai, Norifumi	ICW-C1-6, ICW-B6-2, W41-2, P3-015	Shigemitsu, Yoshika	W9-6, W66-2, P3-182
Sawano, Hiroshi	<b>P1-089</b>	Shigemizu, Sanae	W56-4, P1-121, P1-247
Schett, Georg	<b>IS2-4, ES2-2</b>	Shigesaka, Minoru	W68-5, P1-246, P3-186, P3-214
Schlichting, Douglas	W69-4	Shigeyama, Yukio	<b>P3-143</b>
Segal, Mark	P2-021	Shikano, Kotaro	W28-6, W42-1, W59-2, W76-6, P1-104, <b>P1-146</b> , P2-033, P2-034
Segawa, Seiji	W14-2, W40-2, W40-4, <b>P1-168</b> , P3-039	Shima, Natsuki	<b>W3-1</b>
Seki, Kazushige	<b>P1-119</b> , P2-067, P2-088	Shima, Yoshihito	ICW-B4-2, W11-2, <b>W78-4</b> , P1-193, P1-255
Seki, Masayuki	W10-5, W17-3, W53-3, P2-130, P3-002	Shimada, Hiromi	W9-4, W28-4, W33-6, W34-3, <b>W61-6</b> , W65-6, P1-009, P1-237, P3-222
Seki, Shinya	P1-028, P1-235, P1-239, P2-023, P2-148, P3-086	Shimada, Kota	<b>W13-1</b> , W42-3, W46-3, W64-1, P1-076, P1-216, P2-006, P2-056, P2-059, P2-260, P3-233
Sekigawa, Iwao	W17-6, W79-5, W81-6, P1-163, P1-233, P2-149, P3-161, P3-201, P3-226	Shimada, Wataru	<b>W36-6</b> , P3-100, P3-111
Sekiguchi, Akiko	W32-5	Shimada, Yoichi	W75-2, W83-5, P1-085, P1-120, P1-149, P2-090, P2-094, P2-096, P3-027, P3-029, P3-082, P3-137
Sekiguchi, Masahiro	S6-4, W12-6, W41-6, W43-2, W48-1, <b>W56-2</b> , W56-3, P1-152, P1-171, P2-166, P2-173, P2-175, P3-116, P3-204	Shimada, Yuki	W60-1, P1-249, P2-118
Sekiguchi, Masayuki	W39-2, W63-4, P1-041	Shimamoto, Keiko	W68-5, P1-246, P3-186, P3-214
Sekiguchi, Yukio	P1-217	Shimamura, Sanae	ICW-C2-6, W11-4, W69-2, W69-3
Sekimoto, Tomohisa	P3-021	Shimamura, Yoshiko	W33-2, P1-169, P1-196, P2-196, <b>P3-199</b> , P3-213
Sekine, Akinari	W21-6, W48-5, W78-6, P2-107	Shimane, Kenichi	P2-043, P2-138
Sekita, Chieko	P1-261	Shimaoka, Yasunori	P2-036
Sekiya, Fumio	W73-2, P1-016, P1-017	Shimazu, Hideki	W21-2, W59-5, P1-240, P2-142, P3-152
Sendo, Sho	W13-6, W17-5, <b>W34-1</b> , W41-4, W78-5, P1-202, P3-208	Shimizu, Eiji	ICW-B3-5, W78-3, P2-190
Seno, Takahiro	ICW-C3-4, ICW-B1-6, ICW-B7-5, W19-4, W24-2, <b>W27-5</b> , W40-1, <b>W60-5</b> , P1-236, <b>P2-237</b> , P3-067, P3-153, P3-185	Shimizu, Hayato	P2-208
Seri, Yu	S11-4, W83-1, P2-042	Shimizu, Hideaki	P1-252, P3-005, P3-072
Seta, Noriyuki	ICW-B3-1, W42-4	Shimizu, Hideki	W25-3, W25-4, W80-4, P1-058, P3-046
Seto, Yohei	<b>W19-1</b> , W31-3, W31-5, W35-1, W66-6, P1-261, P2-005, P2-259, P3-050	Shimizu, Hironori	ICW-C8-4, P2-225
Setoguchi, Keigo	W49-4, W64-1, W67-1, W80-5, <b>P2-066</b>	Shimizu, Hisanori	P2-229, P3-003, P3-220
Setoguchi, Takao	W57-4	Shimizu, Jun	<b>S17-4</b> , W35-5
Shabana, Kosuke	<b>W26-4</b> , P3-216	Shimizu, Manabu	W10-2, W10-5, W53-3, W53-4, P2-130, <b>P3-088</b>
Shi, Kenrin	ICW-C6-6, ICW-C6-7, ICW-B4-2, W52-6, W57-5, P1-130, P2-079, P3-045	Shimizu, Masaki	<b>W21-1</b>
Shiba, Hideyuki	W24-3, P1-245, <b>P2-189</b>	Shimizu, Masato	P1-031, P2-085, <b>P2-100</b> , P3-260
Shibanuma, Nao	W18-2, P1-007, P1-059	Shimizu, Miho	P1-203, P2-156
Shibata, Akiko	ICW-C7-3, W16-1, W76-3, P1-033, P1-062, <b>P1-115</b> , P3-262	Shimizu, Takashi	W16-5, W31-2, <b>W32-1</b> , W54-2, P1-127, P2-024, P2-241
Shibata, Hirotaka	P2-162	Shimizu, Tomohiro	<b>W58-5</b>
Shibatani, Masahiko	W45-3	Shimizu, Toshiaki	W22-1, W50-2, <b>W74-3</b> , <b>P2-222</b>
Shibayama, Shiro	W40-2	Shimizu, Toshimasa	W9-6, W22-3, <b>P3-224</b>
Shibuya, Mihoko	ICW-B8-3, W22-4, W28-1, W83-1, P1-260, P2-042	Shimizu, Yoko	W31-1, W31-3, W31-5, W66-6, W67-5, <b>P2-005</b> , P3-050, P3-085
		Shimizu, Yui	W33-3, W61-1, W61-2
		Shimizu, Yuka	ICW-C2-6, W11-4
		Shimmyo, Naoki	ICW-C1-5, W56-2, P1-106
		Shimajima, Yasuhiro	<b>ICW-B2-1</b> , W9-1, W61-4, P1-166
		Shimojo, Naoki	W75-6, P3-209

Shimon, Sakaguchi	<b>RS</b>	Sobue, Yasumori	<b>W12-5</b>
Shimoyama, Kumiko	S1-1, ICW-C3-2, <b>P1-254</b>	Soejima, Yutaro	<b>P2-183</b>
Shinagawa, Satoshi	<b>ICW-C2-7</b>	Soen, Mitsuru	P2-092
Shinagawa, Shoshi	W35-6, P2-182	Soen, Satoshi	<b>MTE10, LS19, ES1-2, P3-100</b>
Shindo, Emiko	W28-6, W42-1, W59-2, W76-6, P1-104, P1-146, P2-033, <b>P2-034</b>	Soga, Takayoshi	P3-063, P3-081
Shindo, Keisuke	W26-4	Sogabe, Ayuko	P1-185, P2-170, P3-125
Shindo, Yasufumi	W60-1, <b>P1-212</b> , P1-249, P2-118	Solomon, L. Bogdan	ICW-C6-3
Shinkawa, Yutaka	ICW-C5-3, P2-157, <b>P2-186</b>	Soma, Masayoshi	W25-6, P1-197
Shinoda, Kei	<b>SW1-4</b>	Son, Yonsu	W68-5, W75-4, W82-2, P1-246, P2-126, P3-186, P3-214
Shinoda, Koichiro	<b>W48-6</b> , P2-195, P2-204, P3-150, P3-159, P3-193	Sono, Yumi	P2-208
Shinohara, Masahiko	P3-114	Sonobe, Keiko	P3-102
Shinohara, Satoshi	W83-1, P2-042, <b>P3-022</b>	Sonobe, Masato	W73-5, P1-111
Shinomiya, Fumio	P1-118	Sonomoto, Koshiro	ICW-B6-6
Shinomiya, Nariyoshi	ICW-B2-6	Suda, Akiko	W32-5, W64-1, P1-049, P2-059, <b>P2-086</b>
Shinomura, Yasuhisa	W33-3	Suda, Masei	P2-229, P3-003, P3-220
Shinozaki, Mikiko	P2-183	Sudo, Akihiro	P3-069
Shinozaki, Yasuyuki	P1-203, P2-156	Sueda, Yuriko	P2-190
Shinya, Hirata	ICW-B5-6	Suehiro, Kenichi	W24-6
Shiohira, Yoshiki	P1-200, P2-187, P3-040, P3-048	Sueishi, Makoto	P3-078
Shioura, Tomone	W1-4, W2-3, W12-3, W36-2	Suematsu, Eiichi	<b>W3-2</b> , W50-3, W64-1, W66-2, W77-6, P2-001, P2-002, P2-009, P2-111, P2-216, P3-070, P3-173, P3-176, P3-178
Shiozawa, Kazuko	<b>W51-1</b> , W81-4, <b>P1-048</b> , P1-098, P3-123	Suematsu, Naoya	P1-010
Shiozawa, Shunichi	W20-6, W51-1, <b>P1-013</b> , P1-048, P1-253, P2-015	Suematsu, Rie	W3-4, W37-2, W66-4, P1-087, P1-108, <b>P1-190</b> , P2-168, P2-214, P3-008
Shirai, Harumi	W22-4, W28-1, <b>W80-5</b> , W83-1, P2-042	Suemori, Koichiro	W51-6, P2-252, <b>P3-180</b>
Shirai, Toshiharu	P3-245	Suenaga, Yasuo	W29-6, <b>W81-5</b> , P2-001, P2-002, P2-009
Shirai, Toshikazu	W64-3, P2-012, P2-013	Suga, Kihumi	P2-268
Shiraishi, Hirokazu	P1-065	Sugano, Eri	W77-5, <b>P2-198</b>
Shiraiwa, Hidetaka	ICW-C4-4, ICW-C9-4, W12-2, W34-6, P2-171, P2-203	Suganuma, Norie	P1-269
Shiraki, Akira	<b>W27-3</b>	Sugata, Ko	W83-2, W83-4
Shiraki, Mayuka	W26-1, <b>W26-5</b>	Sugawara, Eri	W11-4
Shirasawa, Eiji	P3-059	Sugihara, Takahiko	P3-108, P3-200
Shirasugi, Iku	ICW-C5-3, P2-157	Sugii, Shoji	W13-1, W42-3, W46-3, W64-1, <b>LS28-1</b> , P1-076, P1-216, P2-006, P2-059, P2-260, P3-233
Shirota, Yuko	ICW-B8-2, <b>W65-5</b> , P1-215, P1-243	Sugimori, Yusuke	W22-1, <b>W50-2</b>
Shiroto, Katsuaki	W42-3, P2-006, P2-260	Sugimoto, Hideharu	<b>S10-2</b>
Sho, Nobuhiro	W22-2, <b>W48-3</b> , W65-2, W78-1, P1-157, P2-074	Sugimoto, Naoki	W31-1, W31-3, W31-5, W66-6, <b>W67-5</b> , P2-005, P3-050
Shoda, Hirofumi	<b>S11-4</b> , ICW-C5-6, ICW-B3-4, ICW-B3-6, ICW-B7-4, ICW-B8-3, ICW-B9-3, W22-4, W28-1, W66-1, W80-5, W83-1, P2-042	Sugimoto, Toshitsugu	<b>S2-3</b>
Shoda, Naoko	W29-5, W54-4, W76-1, P2-055, P3-129	Sugimoto, Yoshihisa	<b>S10-3</b>
Shoda, Takeshi	<b>W24-3</b> , W27-1, W27-4, W80-3, P2-189, P2-245, P3-228, P3-240	Sugimura, Yusuke	<b>W75-2</b> , W83-5, P1-085, P1-120, <b>P1-149</b> , P2-090, P2-094, P2-096, P3-027, P3-029, P3-082, P3-137
Shoji, Aki	P3-002	Sugino, Masakazu	P3-171, P3-242
Shoji, Kazuhiro	W83-5, P1-085, P1-120, P2-090, P2-094, P2-096, P3-082	Sugioka, Yuko	W7-4, W30-3, W32-3, W37-1, W38-2, W54-1, W58-2, <b>W58-3</b> , W81-3, <b>W83-3</b> , P1-096, P2-016, P2-063, P2-114, P3-014, <b>P3-144</b>
Shoji, Toshiharu	W1-1, W1-2, W1-3, W1-5, W1-6	Sugisaki, Nagachika	W55-2, <b>W73-2</b> , P2-025, P2-047
Shono, Eisuke	P2-052, P3-047	Sugitani, Naohiro	W77-5, <b>P3-107</b>
Shukuzawa, Hiroko	<b>P3-201</b>	Sugiura, Fumiaki	W36-4, P1-114
Singh, Jasvinder A	S17-1		
Smolen, Josef S.	<b>S13-6, IS3-1, ES9-1</b>		
Sobel, Eric S.	P2-021		

Sugiura, Kazumitsu	W51-3, <b>P3-167</b>		<b>P2-130</b> , P3-088
Sugiura, Tomoko	<b>W18-1</b> , P1-037	Suzuki, Hitoshi	P2-014
Sugiyama, Daisuke	P2-143	Suzuki, Jun	W44-3
Sugiyama, Eiji	ICW-B2-2, W14-6, P1-185, P2-170, P3-125	Suzuki, Katsuya	S6-2, ICW-C4-3, ICW-C5-5, ICW-B3-1, ICW-B5-7, ICW-B9-2, W3-6, W13-5, W14-1, W42-4, W44-4, W59-1, W62-2, W62-3, W73-1, P1-077, P3-207
Sugiyama, Kaita	ICW-C4-4, <b>ICW-C9-4</b> , W12-2, W34-6, P2-171, P2-203		W10-4
Sugiyama, Koichi	ICW-C7-4, ICW-C8-2, ICW-C8-3, W4-5, W34-5, W48-4, P2-199, P3-064	Suzuki, Kayo	P1-141, <b>P1-159</b>
Sugiyama, Mai	W25-5	Suzuki, Kazuko	P1-084, P2-136, P3-023
Sugiyama, Takao	W24-1, P3-078	Suzuki, Masahiko	P2-179, P2-197, P3-188
Sugiyama, Yumiko	ICW-C2-1, ICW-C2-2, <b>W7-2</b> , W8-3, W21-4, W32-5, W79-3, W80-2, P2-235	Suzuki, Michita	<b>P1-024</b> , P2-010
Suguro, Toru	S14-3, W39-2, W63-4, P1-041	Suzuki, Miho	<b>P2-251</b>
Sumida, Keiichi	W4-6, W21-6, W48-5, W78-6, P2-107	Suzuki, Mochihito	ICW-C3-2, <b>W38-3</b>
Sumida, Koichi	W46-5, P1-194, <b>P2-193</b> , P3-218, P3-227	Suzuki, Motohiro	<b>W35-5</b>
Sumida, Takayuki	S6-6, S11-4, S15-1, ICW-B1-2, ICW-B3-3, ICW-B4-5, ICW-B5-4, ICW-B6-5, ICW-B7-1, W13-2, W14-2, W28-3, W40-2, W40-4, W49-2, W49-3, W55-3, W62-1, W64-1, <b>LS21</b> , P1-001, P1-019, P1-030, P1-032, P1-168, P2-011, P3-039	Suzuki, Noboru	W3-3, P2-022, <b>P3-028</b> , <b>P3-043</b>
Sumino, Takanobu	W10-2, W10-5, W53-3, W53-4, <b>W53-5</b> , P2-130, P3-088	Suzuki, Satoshi	P2-161, P3-203
Sumita, Yoshiko	<b>P1-188</b> , P2-146, P3-202	Suzuki, Takahiro	ICW-C8-1, W33-1, W34-4, W37-6, W41-5, W64-6, P1-061, P1-160, P2-045, <b>P2-048</b> , P2-205, P3-094, P3-238
Sumitomo, Shuji	S16-4, ICW-B3-4, ICW-B3-6, ICW-B7-3, ICW-B7-4, <b>ICW-B8-3</b> , ICW-B9-3, W22-4, W28-1, W66-1, W83-1, P1-260, P2-042	Suzuki, Takahisa	<b>W8-1</b>
Sumiyoshi, Remi	<b>W22-3</b> , P3-224	Suzuki, Takeshi	S6-6, W13-2, W28-3, W49-2, W49-3, W55-3, P1-030, P1-032
Sunahara, Nobuhiko	W57-4, P1-121, P1-247	Suzuki, Takeshi	W60-3, <b>W62-6</b>
Sunahori Watanabe, Katsue	ICW-C7-4, ICW-C8-2, ICW-C8-3, W4-5, W34-5, W48-4, P2-199, P3-064	Suzuki, Yasunori	W16-3, W51-4, <b>ACL-LS</b> , P1-112, P1-139, P1-181, P2-069, P2-176, P3-158, P3-175, P3-233
Sung, Yoon-Kyoung	ICW-C6-1	Suzuki, Yasuo	ICW-B5-3
Susaki, Kentaro	W9-4, W28-4, W33-6, W34-3, W61-6, W65-6, P1-009, P1-237, P3-222	Syed, Khalid	
Suter, Melissa	ICW-B2-3	<b>T</b>	
Suto, Takahito	ICW-C2-7, ICW-C3-6, <b>W30-4</b> , P1-042, P1-136, P3-013, P3-133	Tabuchi, Yuya	ICW-C5-3, <b>P2-157</b>
Suwabe, Tatsuya	W2-5, W4-6, W21-6, W48-5, W78-6, P2-107	Tachibana, Hideyuki	W60-1, P2-118
Suyama, Yasuhiro	<b>P1-224</b> , P1-263	Tada, Kurisu	<b>W34-2</b> , W68-1, W73-2, W78-2, W80-6, P1-016, P1-195, P2-047
Suzuka, Takayasu	<b>P1-245</b> , P2-245, P3-190, P3-228	Tada, Masahiro	W7-4, W30-3, W32-3, <b>W37-1</b> , W38-2, W54-1, W58-2, W58-3, W81-3, W83-3, <b>P1-096</b> , P2-016, P2-063, <b>P2-114</b> , P3-014
Suzuki, Akari	S11-4	Tada, Yoshifumi	W3-4, W11-1, W21-3, <b>W37-2</b> , W66-4, P1-087, <b>P1-108</b> , P1-190, P2-168, P2-214, P3-008
Suzuki, Akiko	<b>P1-222</b>	Tager, Andrew M	ICW-B2-3, ICW-B2-5
Suzuki, Atsushi	<b>S2-5</b> , P2-161, P3-203	Tago, Mayu	W46-4, P2-008
Suzuki, Ayako	W9-1	Taguchi, Atsushi	P1-148
Suzuki, Chisako	W33-3, W61-1, W61-2	Taguchi, Hiroaki	<b>P1-029</b> , P2-165, P2-250
Suzuki, Daisuke	<b>S1-1</b> , ICW-C3-2, W38-3, P1-254, P3-179	Taguchi, Koichiro	W68-6, <b>P1-191</b> , P3-243
Suzuki, Eiji	P2-185, <b>P3-252</b>	Taguchi, Masashi	W72-5
Suzuki, Gen	W10-2, W10-5, W53-3, W53-4,	Taguchi, Toshihiko	P1-119, P2-067, P2-088
		Tahara, Koichiro	W46-4, P2-008
		Tahara, Masahiro	W14-2, W40-2, W40-4, <b>P1-019</b> , P3-039
		Tahara, Masamichi	<b>P1-256</b>
		Taira, Mariko	<b>P1-037</b>
		Tajika, Tsuyoshi	ICW-C2-7
		Tajima, Yusa	W28-2
		Tajiri, Morihiro	W9-2, P1-175, P2-231

Takabayashi, Katsuhiko	<b>W55-6, P3-122</b>	Takahei, Tamio	W74-2
Takada, Miki	ICW-B3-5	Takahi, Koichiro	<b>W82-1</b> , P1-229, P3-017
Takada, Naoki	<b>W58-2</b>	Takahira, Naonobu	P3-130
Takagi, Haruki	W36-3, P2-092	Takai, Chinatsu	ICW-B7-1, W4-4, W6-6, W41-1, <b>W44-1</b> , W57-6, W79-1
Takagi, Haruna	S17-6	Takai, Noriko	P3-042
Takagi, Hideki	W2-2, W23-3, W36-2, W36-4, W38-5, <b>P1-057</b> , P1-114	Takai, Shinro	W55-4, P1-137, P3-065
Takagi, Kae	W64-2, W77-1, <b>W77-3</b> , P1-167, P1-219	Takaichi, Kenmei	W2-5, W4-6, W21-6, W48-5, W78-6, P2-107
Takagi, Kenji	W28-6, W42-1, P1-033, P1-104, P2-034	Takajo, Ichiro	P1-156
Takagi, Michiaki	MTE8, ICW-C1-1, W10-6, W53-6, W81-1, P1-094, P1-134, P1-141, P3-089	Takajo, Katoko	P1-156
Takagishi, Kenji	ICW-C2-7, ICW-C3-6, W30-4, P1-042, P1-136, P1-268, P3-013, P3-133	Takaki, Ayako	W17-1, W17-4, W20-4, W64-5, P1-210
Takahama, Soichiro	W3-2, W50-3, W77-6, P2-111, P2-216, P3-070, P3-176, P3-178	Takakubo, Yuya	<b>ICW-C1-1</b> , W10-6, W53-6, W81-1, P1-094, P1-134, <b>P1-141</b> , P3-089
Takahara, Daiichiro	ICW-C1-1, W53-6, <b>P3-089</b>	Takamatssu, Ryo	W39-2, W63-4, P1-041
Takahashi, Chihiro	W8-6	Takamatsu, Hisanori	P1-031, P2-085, P3-260
Takahashi, Hidenori	W28-3, W49-2, <b>W49-3</b> , W55-3, P1-030, P1-032	Takamatsu, Hyota	IS2-2
Takahashi, Hiroki	<b>EL19</b> , W21-3, W33-3, W61-1, W61-2	Takamatsu, Mayuko	P2-118
Takahashi, Hiroshi	W52-4, P2-043, P2-138	Takamura, Akito	<b>S4-3</b> , W50-5
Takahashi, Hiroyuki	S6-6, ICW-B4-5, ICW-B5-4, W28-3, W49-2, W49-3, W55-3, <b>W62-1</b> , P1-030, P1-032, P2-011	Takamura, Hiroshi	W10-1, W71-4
Takahashi, Kazuo	<b>P1-151</b>	Takanashi, Tetsuo	P1-034, <b>P1-073</b>
Takahashi, Kengo	<b>W57-4</b>	Takane, Yuki	P3-206, <b>P3-210</b>
Takahashi, Kenji	W55-4, P1-137, <b>P3-065</b>	Takano, Kyoko	P2-179, P2-197, P3-188
Takahashi, Kentaro	P1-109, P1-248	Takaoka, Hirokazu	W61-5, P3-056, <b>P3-170</b>
Takahashi, Kozo	P2-064	Takaoka, Hiromitsu	<b>W19-6</b> , P2-129, P3-055
Takahashi, Kyoko	W25-5	Takasaki, Yoshinari	W3-3, W17-6, W23-1, W34-2, W44-3, W55-2, W64-1, W68-1, W69-2, W69-3, W73-2, W78-2, W80-6, W81-6, P1-015, P1-016, P1-017, P1-093, P1-150, P1-162, P1-163, P1-187, P1-195, P1-233, P2-022, P2-025, P2-047, P2-149, P2-249, P3-028, P3-043, P3-161, P3-196, P3-201, P3-226
Takahashi, Naomi	P2-262	Takasawa, Naruhiko	<b>P1-217</b>
Takahashi, Nobunori	ICW-C1-3, <b>ICW-C3-1</b> , <b>ICW-C3-3</b> , W1-4, W2-2, W2-3, W11-6, W12-3, W12-4, W12-5, W16-4, W19-5, W23-3, W36-1, W36-2, W36-4, W38-5, W39-6, P1-043, P1-050, P1-067, P1-097, P1-099, P1-100, P1-114, P1-138, P2-004, P2-119, P2-125, P2-145, P3-012, P3-020	Takase, Kan	<b>P3-058</b>
Takahashi, Nobuyuki	P2-253	Takashima, Chie	P2-032
Takahashi, Reiko	W6-1, W19-2, W24-5, <b>P1-014</b>	Takaso, Masashi	P3-130
Takahashi, Ryo	W5-6, W60-4, GES-2, P1-235, P1-239, P2-148, P2-219, P3-086	Takasugi, Kiyoshi	ICW-B2-2, W27-2, P2-105, P3-034
Takahashi, Sari	<b>W81-2</b>	Takasugi, Koji	<b>W11-3</b> , W45-1, W56-5, W73-3, P1-252, P3-005, P3-072, P3-117
Takahashi, Satoru	ICW-B1-2, ICW-B3-3, W40-4, P1-019	Takata, Miki	<b>W78-3</b> , P2-190
Takahashi, Shigekazu	P1-220	Takatori, Kyohei	W18-5
Takahashi, Soshi	<b>W13-6</b> , W17-5, W34-1, P3-208	Takatori, Sayaka	W18-5
Takahashi, Takayuki	W25-4, W80-4	Takatori, Shino	P1-033
Takahashi, Toshiya	SW1-5	Takatsuka, Kazutaka	P2-092
Takahashi, Yasufumi	W25-5	Takayama, Maki	W68-4, P1-018, P2-213, P2-218, <b>P2-227</b>
Takahashi, Yoshiko	W62-4	Takayanagi, Hiroshi	<b>EL12</b>
Takahashi, Yuichi	ICW-C1-2, P2-052, <b>P2-068</b> , P3-047	Takayanagi, Kazunobu	P2-267
Takahashi, Yuko	W22-1, W50-2, W74-3, P1-123, <b>P2-020</b> , P2-222, P3-157	Takazawa, Yuji	S3-1
		Takebe, Ken	P1-048, P1-098, <b>P2-128</b> , P3-123
		Takeda, Akira	P2-229
		Takeda, Jun	W4-3, P2-108, P2-167
		Takeda, Koichi	W59-4, P3-198
		Takeda, Tomoki	P3-174
		Takeda, Tsuyoshi	W47-5

Takeda, Yuki	<b>P2-127</b>	Takizawa, Naoho	W30-2, W37-3, P2-201, <b>P3-009</b>
Takei, Hirofumi	ICW-C7-3, W16-1, <b>W76-3</b> , P1-033, P1-062, P1-115, P3-262	Takizawa, Yasunobu	W49-4, <b>W67-1</b> , P2-066
Takei, Hiroshi	<b>ICW-C5-5</b>	Tam, Lai Shan	ICW-B8-5, ICW-B9-4
Takei, Masami	ICW-C4-4, ICW-C9-4, W12-2, W34-6, P1-022, P2-171, P2-203, P3-024	Tamai, Akira	P3-249
Takei, Syuji	<b>EL21</b> , W21-3, W23-1, W26-2, W26-3, W26-6, W69-2, W69-3, SW2-6	Tamai, Hiroshi	W26-4, P1-122, P3-078, P3-216
Takemori, Hiromitsu	<b>P1-080</b> , P1-214, P3-097	Tamai, Mami	ICW-C1-2, ICW-C8-1, W22-6, W33-1, W34-4, W37-6, W41-5, W64-6, <b>P1-061</b> , P1-160, P2-045, P2-048, P2-205, P3-094, P3-238
Takemoto, Reika	W79-4, P1-158	Tamaki, Shigenori	W28-5, <b>W42-5</b> , W46-6, W76-4, W76-5, P2-140
Takemoto, Saori	<b>W81-4</b>	Tamaki, Yasunobu	ICW-C1-1, W10-6
Takemoto, Toki	ICW-C1-3, W12-3, W12-4, W12-5, W19-5, <b>W23-3</b> , W36-1, W39-6, P1-043, P1-067, P1-097, P1-138, P2-119, P2-125, P3-012	Tamechika, Shinya	W23-6, W54-6, P3-115, <b>P3-225</b>
Takemura, Masao	P2-038	Tamimoto, Yasuhiro	P1-119
Takenaka, Sayaka	ICW-C2-3, ICW-C2-4, <b>ICW-C5-4</b> , ICW-C7-2, P3-004	Tamura, Hiroaki	P2-065, P2-177, <b>P3-237</b>
Takeno, Mitsuhiro	ICW-C2-1, ICW-C2-2, W8-3, W21-4, W32-5, W64-4, <b>W68-2</b> , P2-235	Tamura, Masao	P2-242, <b>P3-166</b> , P3-244
Takenouchi, Kenji	W55-4	Tamura, Naoto	<b>S5-5</b> , <b>MTE3</b> , W34-2, W44-3, W55-2, W68-1, W69-2, W69-3, W73-2, W78-2, W80-6, <b>LS17</b> , P1-015, P1-016, P1-017, P1-162, P1-187, P1-195, P2-025, P2-047, P2-249, P3-196
Takeshima, Yusuke	<b>W28-1</b>	Tamura, Yasuyuki	P1-268, P2-099, P3-013
Takehita, Hikaru	P1-025, P3-217, P3-219	Tamura, Yuko	<b>MTE8</b>
Takehita, Masaru	ICW-B3-1, ICW-B5-7, ICW-B9-2, <b>W14-1</b> , W62-2, W73-1	Tan, Ronald	<b>ICW-C6-5</b>
Takeuchi, Akiteru	W6-2	Tanabe, Manabu	W68-3, P3-085
Takeuchi, Fujio	W83-1, P2-042	Tanabe, Yujiro	P1-025, P3-217, P3-219
Takeuchi, Kimihiko	P1-042, P1-268	Tanaka, Akihiko	S6-1
Takeuchi, Takao	W56-2	Tanaka, Akihiro	W68-5, P1-246, P3-186, P3-214
Takeuchi, Tohru	W24-3, W27-1, W27-4, W80-3, P1-165, P1-245, P2-027, P2-123, P2-152, P2-172, P2-189, P2-245, P3-051, P3-120, P3-190, P3-212, P3-228, P3-240	Tanaka, Atsushi	W17-1, W17-4, W20-4, W47-1, W47-2, W50-6, W64-5, P1-210, P2-202
Takeuchi, Tsutomu	S6-2, <b>S7-2</b> , <b>EL4</b> , SW1-2, <b>SW2-4</b> , ICW-C4-2, ICW-C4-3, ICW-C5-5, ICW-B3-1, ICW-B5-7, ICW-B9-2, W1-1, W1-2, W1-3, W1-5, W1-6, W3-6, W8-6, W13-5, W14-1, W15-1, W15-2, W15-3, W23-1, W42-4, W44-4, W59-1, W62-2, W62-3, <b>W69-5</b> , W69-6, W70-1, W73-1, W82-5, <b>LS26-1</b> , <b>ES2-1</b> , <b>ES9-3</b> , P1-077, P2-044, P3-207, SW2-6	Tanaka, Ayae	W55-5, P1-083, P3-060, P3-109, P3-113, <b>P3-266</b>
Takeuchi, Yasuhiro	<b>S2-6</b>	Tanaka, Chihiro	W60-6, P1-048
Takeuchi, Yohei	W9-4, W28-4, W33-6, W34-3, W61-6, <b>W65-6</b> , P1-009, P1-237, P3-222	Tanaka, Dai	P2-076
Takeuchi, Yusuke	<b>P1-076</b>	Tanaka, Eiichi	W5-5, W31-1, <b>W31-3</b> , <b>W31-5</b> , W66-6, W67-5, LS30-1, P1-244, P2-005, P3-050
Takezaki, Shunichiro	<b>W51-5</b>	Tanaka, Eriko	ICW-C4-6, <b>W16-5</b> , W31-2, W32-1, W54-2, P1-127, P2-024, P2-241
Takezaki, Tomoko	W26-2, W26-3, W26-6	Tanaka, Hayate	<b>P1-253</b>
Taki, Hirofumi	W48-6, P2-195, P2-204, P3-132, P3-150, P3-159, P3-193	Tanaka, Hiroaki	<b>W77-2</b>
Taki, Naoya	W71-6	Tanaka, Hiroshi	P1-119
Takigawa, Naohide	P2-097, P3-095	Tanaka, Hirotoshi	W18-6
Takiguchi, Maiko	W62-2, W62-3	Tanaka, Ikuko	W28-5, W42-5, <b>W46-6</b> , <b>W76-4</b> , <b>W76-5</b> , <b>LS15-2</b> , P2-140
Takikura, Terumi	P2-257	Tanaka, Junichi	P3-254
		Tanaka, Junji	W8-4
		Tanaka, Katsunori	<b>W21-5</b>
		Tanaka, Keisuke	P1-024, P2-010
		Tanaka, Masao	ICW-C8-4, W56-2, P1-208, P2-225
		Tanaka, Masato	S10-3
		Tanaka, Michi	S4-3, W29-2
		Tanaka, Nahoko	W28-6, W42-1, W59-2, W76-6, P1-104, P1-146, P2-033
		Tanaka, Sakae	<b>S2-4</b> , <b>IS1-2</b> , <b>EL15</b> , W2-1, W10-1, W29-5, W54-4, W63-2, W76-1, W83-6, <b>ES5-2</b> , P2-055, P3-129

Tanaka, Shin	ICW-C9-2, ICW-C9-3, W49-6, <b>P2-021</b>	Tatematsu, Naoe	<b>P1-128</b>
Tanaka, Sumiaki	W22-2, W48-3, W65-2, W78-1, <b>LS2</b> , LS13, P1-157, P2-074	Tawada, Kaneaki	P2-084, <b>P3-136</b>
Tanaka, Toshio	ICW-B4-2, W11-2, P1-255	Taykayama, Yoshihiro	P2-049
Tanaka, Yasuhiro	P3-091	Tazaki, Naotaka	<b>W45-5</b>
Tanaka, Yasuhito	S12-5, ICW-C1-5, P1-106, P2-268	Terabe, Kenya	ICW-C1-3, W1-4, W2-3, W12-3, W12-4, W12-5, W19-5, W23-3, W36-1, W39-6, P1-043, P1-050, P1-067, P1-097, P1-100, P1-138, P2-125, P3-012
Tanaka, Yasushi	W81-4, P1-048, P1-098, P3-123	Terada, Kaoru	W20-1, P1-063, P1-269, P2-178, P3-006
Tanaka, Yoshiya	S4-1, S6-6, <b>S7-1</b> , S16-3, <b>IS3-4</b> , <b>SW2-6</b> , ICW-C1-6, ICW-C3-5, ICW-C9-2, ICW-C9-3, ICW-B1-3, ICW-B6-2, ICW-B6-6, ICW-B7-7, ICW-B8-1, ICW-B9-1, W1-1, <b>W1-2</b> , <b>W1-3</b> , W1-5, W1-6, W7-1, W14-3, <b>W15-1</b> , <b>W15-2</b> , <b>W15-3</b> , W15-4, W23-1, W37-4, W38-6, W41-2, W43-3, W49-6, W55-1, <b>W69-4</b> , W69-5, <b>W69-6</b> , <b>W70-1</b> , W70-4, W77-2, <b>ES9-2</b> , P1-005, P1-086, P3-015, P3-038	Terada, Makoto	P2-242, P3-166, P3-244
Tanaka, Yuki	ICW-B1-2, ICW-B3-3, <b>ICW-B7-1</b> , W13-2, P1-001, <b>P2-262</b>	Terada, Yoshio	S5-6, W33-2, P1-169, P1-196, P2-196, P3-199, P3-213
Taneichi, Koji	P2-052, P3-047	Terai, Chihiro	P1-227
Tani, Kenji	P1-118	Terakubo, Hisashi	<b>P3-256</b>
Tani, Mei	W22-2, W48-3, W78-1, <b>P1-157</b>	Teranishi, Tsuyoshi	W82-2
Tani, Yasuhiro	<b>P1-036</b>	Terao, Chikashi	W30-5, W31-6, W39-4, W59-3, W63-5, W71-3, W71-5, W82-3, P3-036
Taniguchi, Akira	S12-5	Terasawa, Eiichi	P2-258
Taniguchi, Atsuo	<b>S5-2</b> , ICW-C4-1, W19-1, W31-1, W31-3, W31-5, W66-6, W67-5, W75-3, <b>ACL4</b> , P1-261, P2-005, P2-150, P2-259, P3-050	Terashima, Yasuhiro	W45-6, P1-048, P1-098, P2-128, P3-123
Taniguchi, Daigo	W7-6, W19-4, W45-3, W72-4, <b>P2-224</b> , P2-237, P3-016	Teruya, Shuzo	W17-2, W28-1
Taniguchi, Masashi	ICW-C5-3, P2-157	Teshigawara, Satoru	ICW-C4-6, W16-5, W31-2, W32-1, W54-2, P1-127, P2-024, <b>P2-241</b>
Taniguchi, Shinji	W73-5, P1-111	Tezuka, Taro	P1-110, <b>P2-133</b>
Taniguchi, Shoichi	<b>P2-135</b>	Tezuka, Toshifumi	P2-257
Taniguchi, Yoshinori	S5-4, <b>S5-6</b> , W33-2, P1-169, P1-196, P2-196, P3-199, P3-213	The FUTURE Study Groups	ICW-C9-6
Tanikawa, Akiko	<b>SW1-2</b> , SW1-5	Thomas, Ranjeny	<b>S11-2</b>
Tanikawa, Hirotaka	<b>S18-5</b>	Tian, Zhuang	ICW-C7-6
Tanimoto, Takuya	P2-220	Tjärnlund, Anna	S17-1
Tanimura, Kazuhide	ICW-C2-5, P1-031, P2-085, P2-100, P3-260	To, Hideto	<b>P2-073</b>
Tanimura, Shun	W47-5	Tobe, Kazuyuki	W48-6, P2-195, P2-204, P3-150, P3-159, P3-193
Tanji, Kana	W81-6, P1-233, P2-149, P3-161, P3-201, <b>P3-226</b>	Tochihara, Mari	<b>W64-2</b> , P1-167, P1-219
Tasaka, Yuji	P2-070	Tochimoto, Akiko	W48-2, W64-2, W65-3, W77-1, W77-3, <b>P1-167</b> , P1-219
Tasaki, Chiemi	W21-2, W30-1, W59-5, P1-240, P2-031, P2-142, P3-152	Toda, Toshiya	P3-144
Tashiro, Satoko	W3-4, W37-2, W66-4, P1-087, P1-108, P1-190, P2-168, <b>P2-214</b> , P3-008	Todoroki, Yasuyuki	ICW-C9-2, ICW-C9-3, <b>W49-6</b>
Tateishi, Hironori	W18-2, P1-059	Toge, Yasushi	P3-263
Tateishi, Koji	W18-2, P1-048, P1-098, P2-128, P3-123	Tohchika, Taro	MTE8
Tateishi, Mutsuto	W68-3, P3-085	Tohdo, Satoshi	P2-032
Tateishi, Shoko	ICW-C5-6, ICW-B3-4, ICW-B9-3, W75-5, <b>W83-1</b> , <b>P2-042</b>	Tohma, Shigeto	S9-5, S15-1, W2-1, W5-2, W10-1, W13-1, W29-1, W29-4, W29-5, W29-6, W31-2, W41-3, W42-6, W54-4, W64-1, W66-2, W70-5, W71-4, W81-5, W82-1, W83-2, W83-4, P1-183, P1-241, P2-001, P2-002, P2-007, P2-008, P2-009, P2-055, P2-056, P2-059, P2-074, P2-247, P3-001, P3-018, P3-032, P3-112, P3-247
		Tokai, Nao	P3-051, P3-190
		Tokito, Takeshi	P1-119
		Tokuda, Hitoshi	<b>S14-1</b>
		Tokuda, Yukiko	W3-4, W37-2, <b>W66-4</b> , P1-087, P1-108, P1-190, P2-168, P2-214,

Tokuhashi, Yasuaki	P3-008 W10-2, W10-5, W17-3, W53-3, W53-4, W53-5, P2-130	Tsuchida, Yumi	P2-116, P3-040, P3-048, <b>P3-119</b> ICW-B3-4, ICW-B7-4, ICW-B9-3
Tokuhira, Michihide	<b>MTE7</b>	Tsuchiya, Haruka	ICW-B3-4, ICW-B7-4, ICW-B9-3, W28-1, <b>P1-260</b>
Tokunaga, Daisaku	ICW-B7-5, W7-6, W19-4, W40-1, W45-3, W72-4, P2-224, P3-016	Tsuchiya, Masayuki	<b>S7-4</b>
Tokunaga, Kenichiro	W30-2, <b>W37-3</b> , P2-201, P3-009	Tsuchiya, Naoyuki	<b>S15-1, EL13</b> , P2-056, P2-059
Tokunaga, Tadahiro	<b>P2-220</b>	Tsuda, Hiroshi	W44-3
Tokunaga, Takahiro	W5-6, P1-235, <b>P1-239</b> , P2-148, P3-086	Tsuda, Kousaku	W34-1, P2-160, <b>P3-208</b>
Tokura, Masami	<b>P2-248</b>	Tsuda, Naonori	W13-1, W42-3, P1-216, P2-260, P3-233
Tokushige, Atsunori	P1-119, <b>P2-067</b> , P2-088	Tsuda, Reina	W48-6, P2-195, P2-204, P3-150, P3-193
Tomaru, Utano	W25-1, W25-2	Tsuda, Tokutaro	P2-229, P3-003, P3-220
Tomiiita, Minako	W75-6, P3-206, <b>P3-209</b>	Tsuge, Shunsuke	W13-3, W33-4, P3-181, <b>P3-250</b>
Tominaga, Aiko	ICW-C3-4, W24-2, W27-5, W60-5, P1-236, P2-237, P3-067, P3-153, <b>P3-185</b>	Tsugita, Makoto	W33-2, P3-199, P3-213
Tominaga, Masaki	ICW-B3-2, W9-2, P1-175, P2-231	Tsuji, Goh	W41-4, W70-2, W70-3, W78-5, P1-186, P1-202, P2-143
Tomino, Tatsuhito	P1-252, P3-005, P3-072	Tsuji, Hideaki	<b>W63-6</b>
Tomioka, Masao	<b>MTE8</b>	Tsuji, Osahiko	P1-258
Tomita, Tetsuya	S5-4, ICW-B4-2, P2-037	Tsuji, Shigeyoshi	<b>S5-3</b> , S12-3, W54-2, P1-130
Tomita, Tomoko	W8-5, <b>W56-6</b>	Tsuji, Soichiro	ICW-C4-6, W16-5, W31-2, W32-1, W54-2, P1-127, <b>P2-024</b> , P2-241
Tomita, Yoshitsugu	W10-3	Tsuji, Sosuke	ICW-C8-1, W33-1, W34-4, W37-6, W64-6, P2-205, <b>P3-094</b> , P3-238
Tomitani, Natsuki	<b>P2-268</b>	Tsujimoto, Harutoshi	W36-6
Tongu, Kanami	W19-2	Tsujimoto, Kohei	<b>ICW-C5-3</b> , P2-157
Tono, Toshihiro	P1-029, <b>P2-165</b> , P2-250	Tsujimoto, Saki	W68-5, P1-246, <b>P3-186</b> , P3-214
Tonogai, Ichiro	P1-004	Tsujimura, Miho	P3-245
Tonozuka, Norihiko	P3-002	Tsujimura, Shizuyo	<b>P3-038</b>
Torii, Mie	<b>W59-3</b> , W82-3	Tsujino, Emi	<b>P3-071</b>
Torii, Sadakazu	P2-108	Tsukada, Toshiaki	W22-6
Toritsu, Yuichi	<b>P2-210</b>	Tsukahara, Juri	W46-5, P1-194, P2-193, <b>P3-218</b> , P3-227
Toujima, Akihiro	<b>P1-118</b>	Tsukahara, Takayoshi	W80-6, <b>P1-195</b>
Toyama, Shogo	W7-6, W19-4, <b>W45-3</b> , W72-4	Tsukamoto, Hiroshi	W11-1, W17-1, W17-4, W20-4, W21-3, W47-1, W47-2, <b>W50-6</b> , W62-5, W64-5, P1-210, P2-202
Toyoda, Yuko	P2-255, <b>P2-257</b>	Tsukamoto, Masako	<b>W42-4</b>
Toyozumi, Shigeyuki	W15-1, W15-2, W15-3, W15-4	Tsukano, Michishi	W63-3
Toyoshima, Yoichi	W18-3, <b>W75-1</b>	Tsukeoka, Tadashi	P1-084
Toyota, Yukihiro	ICW-C2-1, ICW-C2-2, W7-2, <b>W8-3</b> , W21-4	Tsukida, Mayuko	<b>P3-105</b>
Toyota Tatebe, Noriko	ICW-C7-4, ICW-C8-2, ICW-C8-3, W4-5, W34-5, W48-4, P2-199, P3-064	Tsukui, Daisuke	SW1-3, W6-2, W68-4, P2-213, <b>P2-218</b> , P2-221
Tozawa, Yusuke	W51-5	Tsumiyama, Ken	<b>W20-6</b> , P1-013, P1-048, <b>P2-015</b>
Tschumperlin, Daniel	ICW-B2-3	Tsuneizumi, Yoshikazu	<b>P1-084</b>
Tsuboi, Hideki	S12-3, ICW-B4-2, W16-5, W45-5, W52-6, W54-2, P1-130, P2-079	Tsunemi, Sachi	W12-6
Tsuboi, Hiroto	<b>S6-6</b> , ICW-B4-5, <b>ICW-B5-4</b> , W13-2, W14-2, W28-3, W40-4, W49-2, W49-3, W55-3, W62-1, P1-019, P1-030, P1-032, P2-011, P3-039	Tsuno, Hirotaka	P1-183, P1-241, <b>P2-007</b> , P2-247, P3-001, P3-018, P3-112, P3-247
Tsuboi, Seiji	ICW-C3-2, W12-3, W38-3, W38-5	Tsuno, Manabu	P1-232
Tsuboi, Yoshiai	P3-110	Tsunoda, Shinichiro	W12-6, W21-1, W41-6, <b>W43-2</b> , W48-1, W56-3, P1-152, P1-171, P2-059, P2-166, P2-173, P2-175, P3-001, P3-116, P3-241
Tsubouchi, Yasunori	P3-164, <b>P3-169</b>	Tsuru, Tomomi	W7-1, P2-052, P2-116, P3-047
Tsuchida, Kosei	W28-2	Tsushima, Hiroshi	<b>P1-150</b>
Tsuchida, Marina	P2-248	Tsuzaka, Kensei	<b>P1-052</b> , P1-123
Tsuchida, Naomi	ICW-C2-1, ICW-C2-2, W7-2, W8-3, <b>W21-4</b> , W32-5, W79-3, W80-2, P2-235		
Tsuchida, Tetsuya	<b>EL24</b>		
Tsuchida, Toyomitsu	W39-2, W63-4, P1-041, <b>P1-103</b> ,		

<b>U</b>			
Ubara, Yoshifumi	ICW-B2-2, W2-5, W4-6, W21-6, W33-5, W48-5, W78-6, P2-107	Uno, Yoshihiro	P3-229
Uchida, Teisuke	W28-2, W43-4, <b>P1-198</b> , P2-058, P2-182	Unoda, Kiichi	<b>P3-212</b> , P3-216
Uchida, Yoshio	W52-4, <b>P2-138</b>	Urata, Yukitomo	P2-009, <b>P3-019</b>
Uchimura, Shoichi	P2-116	Urayama, Masakazu	W75-2, W83-5, P1-085, <b>P1-120</b> , P2-090, P2-094, P2-096, P3-027, P3-082
Uchino, Ayumi	W51-2, W73-4, P1-065, P3-033	Urushidani, Yoshinori	W6-3, W67-6
Uchiyama, Katsufumi	P3-130	Ushida, Takahiro	<b>S3-4, MTE15</b>
Uchiyama, Kazuhiko	W5-4, <b>W29-3</b>	Ushigusa, Takeshi	<b>W41-5</b>
Uda, Miyabi	W59-3, <b>W82-3</b>	Ushikubo, Mari	W28-5, W76-4, W76-5, <b>P2-140</b> , P3-206, P3-210
Uechi, Eishi	<b>P1-200</b> , P2-187	Ushio, Kazuyasu	P3-040, P3-048
Ueda, Akira	W11-1, P2-151	Ushio, Tetsuro	<b>P3-128</b> , P3-134
Ueda, Atsuhisa	ICW-C2-1, ICW-C2-2, W7-2, W8-3, W21-3, W21-4, W32-5, W64-4, W79-3, W80-2, P2-235	Uto, Kenichi	W40-3
Ueda, Miwa	<b>W82-4</b>	Uzuki, Miwa	<b>P1-020</b>
Ueda, Naoyasu	P2-151	<b>V</b>	
Ueda, Sho	W17-1, W17-4, W64-5, P1-210	Valdez, Hernan	W15-4
Ueda, Yo	W34-1, P2-160, P3-208	van der Heijde, Désirée	<b>IS3-2, LS14</b>
Ueda, Yusuke	W75-4, <b>P2-126</b>	Vincent, Ludovic	ICW-B2-3
Ueha, Takeshi	<b>P1-040</b>	<b>W</b>	
Uehara, Hisaaki	W81-6	Wada, Jun	ICW-C7-4, ICW-C8-2, ICW-C8-3, W4-5, W34-5, W48-4, P2-199, P3-064
Uehara, Kazunori	P3-255	Wada, Makoto	W32-3
Uehara, Masaaki	W18-6	Wada, Takahiko	W75-4, P2-126
Uehara, Takeaki	W32-5	Wada, Takashi	P1-203, P2-156
Ueki, Kazue	P3-105	Wada, Takuma	W13-4, <b>W60-1</b> , P1-033, P1-249, P2-026, P2-118
Ueki, Masahiro	W51-5	Wada, Tatsuhiko	W48-3, W65-2, W78-1, P1-157, P2-074
Ueki, Naoko	W17-1, W17-4, W20-4, W50-6, W64-5, P1-210	Wada, Yoko	ICW-C6-4, W2-6, W4-4, W6-6, W33-5, W41-1, W44-1, W57-6, W65-4, W79-1, P3-154
Ueki, Yukitaka	<b>MTE11</b> , ICW-C1-2, W7-1, W20-1, W22-6, W37-6, W64-6, <b>P1-063</b> , P1-269, P2-178, P3-006	Wada, Yumiko	P2-123, P2-152, <b>P2-245</b> , P3-190
Uemura, Yuko	<b>W41-4</b> , W70-2, W78-5	Wakabayashi, Hiroki	<b>P3-069</b>
Ueno, Akiko	W43-1, P1-211, P2-112	Wakabayashi, Hiroshi	ICW-C7-4, ICW-C8-2, ICW-C8-3, W4-5, W34-5, W48-4, P2-199, P3-064
Ueno, Kenichi	ICW-B2-1, W9-1, W61-4, <b>P1-166</b>	Wakabayashi, Kuninobu	W5-6, W18-3, W60-4, P1-235, P1-239, P2-023, P3-086
Ueno, Toshiharu	W48-5, <b>W78-6</b> , <b>P2-107</b>	Wakabayashi, Takayuki	W16-3, W51-4, <b>P1-139</b> , P1-181, P2-069
Uesugi, Hiroko	<b>P3-241</b>	Wakamatsu, Ayako	W4-4, W6-6, W41-1, W44-1, W57-6, <b>W79-1</b>
Ueta, Yoichi	P2-014	Wakasugi, Daisuke	ICW-B3-2, W9-2, P1-175, P2-231
Uetani, Masataka	P1-061, P2-045	Waki, Daisuke	W34-1, <b>P2-160</b>
Ukichi, Taro	W6-5, W49-5, P2-113	Wakiguchi, Hiroyuki	W26-2, W26-3, <b>W26-6</b>
Umeda, Masataka	ICW-C8-1, W33-1, W34-4, W37-6, W41-5, <b>W64-6</b> , P1-061, P1-160, P2-045, P2-205, P3-006, P3-094, P3-238	Wakisaka, Takumi	P3-102
Umeda, Naoto	S6-6, ICW-B1-2, ICW-B3-3, ICW-B7-1, <b>W13-2</b> , W28-3, W49-2, W49-3, W55-3, P1-001, P1-030, P1-032	Wakiya, Risa	W9-4, W28-4, W33-6, W34-3, W61-6, W65-6, P1-009, P1-237, <b>P3-222</b>
Umeda, Ryosuke	W41-4, <b>W70-2</b> , W70-3, W78-5, P1-186, P1-202	Wakura, Daisuke	P3-212
Umekita, Kunihiko	<b>ICW-B6-3</b> , P1-156, P2-234	Wakura, Reiko	P2-152, P3-212
Umemura, Kumiko	<b>P2-179</b> , P2-197, P3-188	Wang, Guochun	ICW-B5-5
Umemura, Masayu	W5-6, GES-2, <b>P1-028</b> , P1-235, P1-239, P2-023, P3-086	Wang, Liangwei	W69-5, W69-6
Umezawa, Natsuka	<b>W50-5</b>	Wang, Lisy	W15-2
Umibe, Takeshi	P1-123, P2-095	Wang, Peggy	ICW-B8-1
Uno, Haruka	P1-057	Wang, Qian	<b>ICW-C7-6</b>



Wang, Ting	ICW-B8-6	Yajima, Tsutomu	W23-2, P3-076
Waseda, Kazuyo	P1-266	Yaku, Ai	<b>W24-4</b> , P1-172
Watada, Toshiko	P1-119	Yamada, Akihiro	W27-2, P2-105, P3-034
Watanabe, Eiichiro	<b>P3-245</b>	Yamada, Akira	W25-3, W25-4
Watanabe, Haruki	ICW-C7-4, ICW-C8-2, <b>ICW-C8-3</b> , W4-5, W34-5, W48-4, P2-199, P3-064	Yamada, Chiho	W16-3, W51-4, P1-112, P1-181, P2-176, P3-158, P3-175
Watanabe, Hidetoshi	W83-5, P1-085, P1-120, P2-090, P2-094, P2-096, P3-082	Yamada, Harumoto	<b>S3-2</b> , P2-134
Watanabe, Hideyuki	<b>P2-001</b> , P2-002	Yamada, Hidehiro	S15-1, W21-3, W28-2, W35-6, W43-4, P1-177, P2-058, P2-182
Watanabe, Hirofumi	<b>P1-185</b> , P2-170, P3-125	Yamada, Hirotaka	ICW-C5-2, W3-5, W8-2, <b>W15-6</b> , P1-176, P1-225, P1-265, P2-226
Watanabe, Hiroki	P2-135	Yamada, Hisakata	W17-1, W40-6
Watanabe, Hiroshi	P2-185, P2-211, P3-030, P3-184	Yamada, Kazunori	W4-2, W33-4, W36-3, W44-6, W60-3, W62-6, W67-4, P1-209, P1-242, <b>P2-120</b> , P3-192
Watanabe, Kanako	<b>W47-5</b>	Yamada, Kenkou	W10-2, <b>W10-5</b> , W17-3, <b>W53-3</b> , W53-4, P2-130, P3-088
Watanabe, Kenta	W10-4	Yamada, Kouji	S14-3
Watanabe, Kozo	W81-6, P3-161	Yamada, Kunio	<b>P2-084</b> , P3-136
Watanabe, Mitsuru	P1-252, P3-005, P3-072	Yamada, Masato	P3-196
Watanabe, Naohiro	<b>ACL6</b>	Yamada, Shinsuke	W60-2, P1-251
Watanabe, Norihiko	P1-220	Yamada, Soichi	W44-2, P1-178, <b>P3-080</b> , P3-183
Watanabe, Ryu	ICW-C1-2, ICW-B8-2, W65-5	Yamada, Takashi	P3-085
Watanabe, Takashi	W73-2	Yamada, Teruchika	P3-160
Watanabe, Tatsuo	S18-3, <b>ICW-C1-3</b> , W12-4, <b>P1-138</b> , P3-012	Yamada, Toshiyuki	W6-6, <b>W61-3</b> , W61-4
Watanabe, Tetsuo	P2-064	Yamada, Yusuke	<b>P1-163</b> , P2-025, <b>P2-047</b>
Watanabe, Toshiyuki	ICW-C2-6, W11-4, W32-5, P2-086	Yamagata, Kaoru	ICW-B6-2, ICW-B6-6, ICW-B7-7, W14-3, W41-2, <b>P1-005</b>
Watanabe, Tsuyoshi	W1-4, W2-2, W36-2	Yamagata, Kunihiro	S15-1
Watanabe, Wataru	W83-5, P1-085, P1-120, P2-090, P2-094, P2-096, P3-082	Yamagata, Mieko	<b>W24-1</b> , W24-6
Watanabe, Yohei	<b>P3-267</b>	Yamaguchi, Akinori	W25-5
Watanabe, Yuko	W61-5, P2-108, P3-056	Yamaguchi, Kenichi	P2-229, P3-003, <b>P3-220</b>
Watanuki, Satoshi	W13-1, W42-3, W46-3, P1-216, <b>P2-006</b> , P2-260, P3-233	Yamaguchi, Kensuke	ICW-B7-4
Watari, Mihoko	P1-266	Yamaguchi, Masao	<b>AP</b>
Werth, Victoria P	S17-1	Yamaguchi, Norihiko	P1-127, <b>P3-246</b>
Weston, Amanda	ICW-B5-3	Yamaguchi, Rei	W31-1, W31-3, W31-5, <b>W66-6</b> , W67-5, P2-005, P3-050
Weyand, Cornelia M	IS2-3	Yamaguchi, Satoshi	W48-6, P2-195, P2-204, P3-150, P3-159, <b>P3-193</b>
Wong, Chun Kwok	ICW-B8-5, ICW-B9-4	Yamaguchi, Yukie	P1-151
Wu, Zhenzhen	ICW-B2-4	Yamaguchi, Yukinari	W46-5, <b>P1-194</b> , P2-193, P3-218, P3-227
<b>X</b>		Yamaguchi, Yumi	W83-1, P1-260, P2-042, <b>P2-256</b>
Xiaofeng, Zeng	ICW-C9-1	Yamaguchi, Yuta	ICW-C4-6, P1-226, P2-172, P2-174, <b>P2-228</b>
Xu, Dong	ICW-B8-6	Yamahana, Junya	<b>P2-181</b>
<b>Y</b>		Yamaide, Akiko	P3-209
Yabe, Hiroki	<b>P1-227</b>	Yamaide, Fumiya	W75-6
Yabe, Yuichiro	W1-4, <b>W11-6</b> , W12-3, W12-5, W36-2, W36-4, W38-5, P1-114	Yamaji, Ken	W34-2, W44-3, W55-2, W68-1, W73-2, W78-2, W80-6, P1-015, P1-016, P1-017, P1-162, P1-187, P1-195, P2-025, P2-047, P2-249, P3-196
Yabuki, Akiko	W72-5	Yamakawa, Noriyuki	W30-5, W31-6, W39-4, W63-5, W71-3, W71-5, P1-140, P3-036
Yaegaki, Makoto	<b>P3-124</b>	Yamamoto, Aihiro	ICW-C3-4, ICW-B1-6, ICW-B7-5, W24-2, W27-5, W40-1, W56-2, W60-5, <b>P1-236</b> , P2-237, <b>P3-067</b> ,
Yagishita, Mizuki	<b>W28-3</b> , W49-2, W49-3, W55-3, P1-030, P1-032		
Yagita, Masato	ICW-C5-3, P2-157, P2-186		
Yago, Toru	W58-4, W69-1, P2-215, <b>P3-146</b>		
Yahagi, Ayano	P1-026		
Yahikozawa, Hiroyuki	P2-155, P2-200		
Yajima, Hidetaka	W33-3		
Yajima, Hiroki	<b>S18-3</b>		
Yajima, Nobuyuki	W5-6, W60-4, P3-086		
Yajima, Takahiro	<b>P3-189</b>		

	P3-153, P3-185	Yamasaki, Masaomi	<b>W74-5, P1-081</b> , P1-177
Yamamoto, Kazuhiko	<b>PL</b> , S11-4, S16-4, SW1-5, SW2-7, ICW-C5-6, ICW-B3-4, ICW-B3-6, ICW-B7-3, ICW-B7-4, ICW-B8-3, ICW-B9-3, W1-1, W1-2, W1-3, W1-5, W1-6, W17-2, W22-4, W28-1, W40-5, W66-1, W75-5, W79-6, W80-5, W83-1, P1-260, P2-042	Yamasaki, Satoshi	<b>W14-6</b> , P1-185, P2-170, P3-125
Yamamoto, Kengo	W72-6	Yamasaki, Takahito	<b>P2-091</b>
Yamamoto, Kenji	P1-119	Yamasaki, Tetsuro	W72-4, P3-016
Yamamoto, Manabu	P1-119	Yamasaki, Yoshioki	<b>W28-2</b> , W35-6, W43-4, <b>LS32</b> , P1-177, P2-058, P2-182
Yamamoto, Masahiro	W3-2, W50-3, W77-6, P2-111, P2-216, P3-070, P3-173, P3-176, P3-178	Yamasaki, Yuichi	W26-3
Yamamoto, Motohisa	<b>W33-3</b> , W33-5, W61-1, W61-2	Yamashita, Hiroyuki	<b>W22-1</b> , W50-2, W74-3, P1-123, P2-222, P3-157
Yamamoto, Shotaro	P2-220	Yamashita, Misuzu	W11-3, W45-1, <b>W56-5</b> , W73-3, P3-117
Yamamoto, Takeshi	W75-6	Yamashita, Naoko	ICW-C2-4
Yamamoto, Takuaki	P3-121	Yamate, Ryosuke	<b>P3-182</b>
Yamamoto, Tatsuhiko	W28-6, <b>W42-1</b> , W59-2, W76-6, P1-104, P1-146, P2-033, P2-034	Yamatoh, Tsuyoshi	W26-2, W26-3, W26-6
Yamamoto, Wataru	W11-3, W30-5, W31-6, W39-4, W45-1, W56-5, W59-3, W63-5, W71-3, W71-5, W73-3, W82-3, P3-117	Yamauchi, Kohei	W9-5, P1-124, P2-153, P2-169
Yamamoto, Yusuke	W46-4, P3-002	Yamauchi, Masaki	S6-1
Yamamoto, Yuzuru	P1-170, P1-231, P2-143, <b>P3-155</b>	Yamauchi, Naofumi	<b>P3-066</b>
Yamamoto-Fukuda, Tomomi	W62-4	Yamauchi, Nobuaki	P1-222
Yamamura, Masahiro	W43-1, P1-211, P2-112	Yamauchi, Yasutaka	P2-254
Yamamura, Takashi	IS2-5	Yamazaki, Daiki	<b>W25-5</b>
Yamamura, Yuriko	W43-1, <b>P1-211</b> , P2-112	Yamazaki, Hajime	W33-5, P3-154
Yamana, Jiro	P1-070, P2-077, <b>P2-164</b> , P3-040	Yamazaki, Hayato	W31-4
Yamana, Seizo	P1-070, P2-077, P2-164	Yamazaki, Hideshi	<b>P1-034</b> , P1-073, P3-040, P3-048
Yamanaka, Hajime	P1-122, <b>P3-078</b>	Yamazaki, Ikuko	W45-2
Yamanaka, Haruo	<b>P3-168</b>	Yamazaki, Ryutaro	W55-5, P1-083, <b>P3-109</b> , P3-113, P3-266
Yamanaka, Hisashi	S1-3, S5-2, <b>SW2-3</b> , ICW-C4-1, W1-1, W1-2, W1-3, <b>W1-5, W1-6</b> , W5-5, W15-2, W19-1, W23-1, W31-1, W31-3, W31-5, W35-1, W48-2, W58-4, W64-2, W65-3, W66-6, W67-5, W69-1, W74-6, W75-3, W77-1, W77-3, W77-5, <b>LS3, LS30-1</b> , P1-154, P1-155, P1-167, P1-219, P1-244, P1-261, P2-005, P2-150, P2-198, P2-215, P2-217, P2-259, P3-050, P3-107, P3-146, SW2-6	Yamazaki, Takahito	W6-3, W67-6
Yamanaka, Kenjiro	W3-3, W55-2, P1-093, P2-022, P3-028, P3-043	Yamazaki, Tetsu	W32-5
Yamanaka, Ryutaro	W79-4, P1-158, <b>P1-201</b> , P1-238	Yamazaki, Yuri	P1-187, P2-249
Yamanaka, Takao	<b>P3-074</b>	Yan, Xiyun	ICW-B2-4, ICW-B9-5
Yamane, Takashi	W60-6, P1-048	Yanagida, Tamiko	P1-018, P2-213, P2-218
Yamanishi, Shingo	<b>P1-025</b> , P3-217, P3-219	Yanagisawa, Maiko	W60-1, P2-118
Yamano, Yoshihisa	W35-5, W35-6, P1-003	Yanagisawa, Masahiko	W17-3
Yamaoka, Kunihiro	<b>EL14</b> , ICW-C3-5, ICW-C4-3, ICW-C5-5, ICW-B1-3, ICW-B3-1, ICW-B5-7, ICW-B6-6, W8-6, <b>W15-4</b> , W42-4, W77-2, <b>LS7-1, ES8-2</b> , P3-207	Yanagisawa, Takao	W43-5, P3-223
Yamasaki, Akira	ICW-B3-5, W78-3, P2-190	Yanai, Ryo	<b>W5-6</b> , W60-4, <b>P2-023</b> , P2-046, P3-086
Yamasaki, Hitoshi	W51-6, P2-252, P3-180	Yang, Kunitaka	W83-5, P1-085, P1-120, P2-090, P2-094, P2-096, P3-082
		Yang, Kwangseok	W44-3
		Yang, Suran	ICW-C1-1, W10-6, W53-6, W81-1, P1-094, P1-141, P3-089
		Yano, Koichiro	<b>S12-4</b> , W72-1, P3-055
		Yano, Shintaro	<b>P3-114</b>
		Yano, Tomohiro	W21-2, W30-1, W59-5, P1-240, P2-031, P2-142, P3-152
		Yano, Yuya	P2-118
		Yashiro, Makiko	<b>P2-211</b> , P3-030, P3-184
		Yasuda, Masahiko	P1-150
		Yasuda, Shinsuke	<b>S8-4</b> , ICW-C2-6, W11-4, <b>W69-2</b> , W69-3
		Yasuda, Tadashi	<b>ICW-B6-4</b>
		Yasuda, Taketoshi	<b>W10-4</b>
		Yasui, Tetsuro	W2-1, W29-5, W54-4, W76-1, P2-055, P3-129
		Yasukawa, Masaki	W51-6, P2-252, P3-180
		Yasumi, Takahiro	EL6
		Yasuoka, Hidekata	ICW-C4-3, ICW-B3-1, ICW-B5-7, W59-1

Yazaki, Masahide	W9-1		P2-172, P2-189, P3-051, P3-190,
Yo, Noriaki	<b>W60-6</b> , P1-048		P3-212, P3-228, P3-240
Yoda, Koichiro	W60-2, P1-251	Yoshida, Tomohiko	<b>P1-068, P1-102</b> , P3-040, P3-048
Yoda, Maki	W60-2, P1-251	Yoshida, Tomohiro	W45-1
Yokoe, Isamu	ICW-C4-4, W34-6, <b>P3-024</b>	Yoshida, Yoshihiro	W60-1, <b>P1-173</b> , P1-212, P1-249,
Yokogawa, Naoto	<b>S1-2, SW1-5</b> , W13-1, W42-3, W46-3, P1-076, P1-216, P2-006, P2-260, P3-233		P2-118
Yokoi, Syunsuke	P2-179, P3-188	Yoshida, Yuji	IS2-2, <b>ICW-B4-2</b>
Yokosawa, Masahiro	S6-6, W14-2, W28-3, W40-2, W40-4, W49-2, W49-3, W55-3, P1-019, P1-030, P1-032, <b>P3-039</b>	Yoshida, Yusuke	W14-6, <b>P3-010</b>
Yokota, Akira	W56-2	Yoshie, Hiromasa	P2-102
Yokota, Atsushi	<b>P3-148</b>	Yoshifuji, Hajime	<b>S17-2</b> , W50-1, W63-6, W65-1
Yokota, Eisuke	W73-4, P2-098, P2-115, P2-147, P3-035, P3-239	Yoshiga, Masayuki	W6-5, W49-5, P2-113
Yokota, Kazuhiro	<b>ICW-B1-4</b> , W13-4, W60-1, P1-173, P1-212, P1-249, <b>P2-026</b> , P2-118	Yoshihara, Ken	W25-4, W44-5
Yokota, Toshihiko	ICW-C5-2, W3-5, W8-2, W15-6, P1-176, P1-225, P1-265, P2-226, P2-267	Yoshihara, Ryosuke	W81-4, P1-048, P1-098, P3-123
Yokota, Yutaka	W36-4, <b>W38-1</b>	Yoshihara, Toshio	W62-1
Yokoyama, Hironobu	P1-048, P2-128	Yoshihashi, Yoko	S4-3, W50-5
Yokoyama, Hiroshi	<b>P2-109</b>	Yoshihiro, Kyoko	P3-032
Yokoyama, Hitoshi	<b>S8-1</b>	Yoshii, Ichiro	<b>W32-6</b> , W56-2, <b>P1-051, P2-029,</b> <b>P3-049</b>
Yokoyama, Waka	W29-2, W31-4	Yoshikawa, Ayaka	P2-027, P2-123, <b>P3-051</b>
Yokoyama, Yuichi	W12-6, W41-6, W43-2, W48-1, W56-3, P1-152, P1-171, <b>P2-166</b> , P2-173, P2-175, P3-116	Yoshikawa, Hideki	ICW-C6-6, ICW-C6-7, W46-2, W57-2, W57-5, P1-130, P2-037, P2-079
Yokoyama, Yusuke	<b>W50-4</b>	Yoshikawa, Maiko	<b>ICW-B8-1</b> , ICW-B9-1, W14-3, W37-4, W38-6, W43-3
Yoneda, Kazuo	P2-240	Yoshikawa, Norie	<b>W83-2</b> , W83-4
Yonemoto, Yukio	ICW-C2-7, ICW-C3-6, W30-4, P1-042, <b>P1-136</b> , P1-268, P3-013, P3-133	Yoshikawa, Noritada	<b>W18-6</b>
Yonezawa, Rika	W6-1, W19-2, <b>W24-5</b>	Yoshikawa, Reo	P1-123
Yonezu, Hiroshi	<b>P2-238, P3-149</b>	Yoshikawa, Takahiro	W12-6, W41-6, W48-1, <b>W56-3</b> , P1-152, P1-171, P2-166, P2-173, P2-175, P3-116
Yong, Hou	ICW-C9-1	Yoshimatsu, Yuki	P2-018
Yoon, Jeong-Hwan	ICW-B6-5	Yoshimi, Ryusuke	ICW-C2-1, <b>ICW-C2-2</b> , W7-2, W8-3, W21-4, W32-5, W64-4, W79-3, W80-2, P2-235
Yorifuji, Hideki	W11-2, P1-193	Yoshimitsu, Makoto	P2-158
Yoshida, Akiko	W44-2, P1-178, P3-080, <b>P3-183</b>	Yoshimoto, Keiichi	<b>P3-249</b>
Yoshida, Akira	W38-4, W70-6, W74-2, P2-060, P3-075, P3-092, P3-093, <b>P3-236</b>	Yoshimoto, Keiko	<b>S6-2</b> , ICW-C4-3, W42-4, W73-1
Yoshida, Hiroaki	P3-105	Yoshimoto, Ryota	W18-5, P2-184, P2-232
Yoshida, Hiroto	P1-024, <b>P2-010</b>	Yoshimura, Ichiro	P3-270
Yoshida, Kazuki	W30-2, W37-3	Yoshimura, Maiko	ICW-C4-6, W16-5, W31-2, W32-1, W54-2, P1-127, P2-024, P2-241
Yoshida, Ken	<b>S11-5</b> , W6-5, W49-5, P1-021, P2-113	Yoshimura, Noriko	<b>EL25</b>
Yoshida, Kenji	W73-4, P2-098, P2-115, P2-147, P3-035, <b>P3-239</b>	Yoshinaga, Tsuneaki	<b>P3-162</b>
Yoshida, Kohsuke	W18-2, P1-007, P1-059	Yoshinaga, Yasuhiko	<b>W5-2</b> , W33-2, W41-3, <b>P1-232</b> , P1-234
Yoshida, Masaaki	P3-040, P3-048	Yoshinari, Hiroko	W43-3
Yoshida, Munehito	P1-259	Yoshinouchi, Takeo	P2-108
Yoshida, Naomi	ICW-B3-2, W9-2, <b>P1-175</b> , P2-231	Yoshinoya, Kiyokazu	P3-246
Yoshida, Shinji	<b>ICW-C4-1</b> , W72-1	Yoshinoya, Sadayoshi	P3-246
Yoshida, Shoji	P1-109, P1-248	Yoshioka, Hiroyuki	<b>W8-4</b>
Yoshida, Shunji	W5-3, W44-2, P1-178, P3-080, P3-183	Yoshioka, Yutaka	ICW-C1-3, W12-3, W12-4, W12-5, W16-4, W19-5, W23-3, W36-1, W39-6, P1-043, <b>P1-067</b> , P1-069, P1-097, P1-138, P2-125, P3-012
Yoshida, Shuzo	W27-1, W27-4, W80-3, P1-165, P1-245, P2-027, <b>P2-123</b> , P2-152,	Yoshitama, Tamami	W7-1, W56-4, P3-040, P3-048
		Yoshitomi, Hiroyuki	W30-5, W31-6, W63-5, W72-3
		Yoshizawa, Seiji	W11-1, <b>P3-248</b>
		Yoshizawa, Shigeru	W11-1, W62-5, <b>P3-032</b>

Yu, David	<b>S5-1</b>
Yu, Di	<b>IS2-1</b>
Yuanfang, Zheng	ICW-C9-1
Yuasa, Shino	P1-118
Yuasa, Takahiro	P1-203, <b>P2-156</b>
Yudoh, Kazuo	W35-5, W35-6, P1-003, P1-011
Yuge, Hidehiko	P3-121
Yukawa, Kazutoshi	W47-4, <b>P1-126, P1-213</b>
Yukawa, Naoichiro	<b>S8-5</b> , W50-1, W63-6, W65-1
Yuki, Hokuto	W10-6
Yukioka, Chikako	P3-042, P3-044, <b>P3-045, P3-052</b> , P3-054
Yukioka, Futoshi	P3-044, P3-052, P3-054
Yukioka, Kumiko	P3-042, P3-044, P3-052, <b>P3-054</b>
Yukioka, Masao	P2-041, P3-042, P3-044, P3-045, P3-052, P3-054
Yumoto, Taeko	W21-2, W59-5, P1-240, P2-142, P3-152
Yunoue, Naoki	ICW-B8-1, ICW-B9-1, W14-3, W38-6
Yura, Akiko	ICW-C4-6, W16-5, W31-2, W32-1, W54-2, P1-127, P2-024, P2-241

## Z

---

Zebaze, Roger M	<b>IS1-4</b>
Zeng, Xiaofeng	ICW-C7-6, ICW-B2-4, ICW-B8-6, ICW-B9-5
Zhang, Heng-Hui	ICW-B8-6
Zhang, Li	ICW-B9-5
Zhang, Lingling	<b>ICW-B2-4, ICW-B9-5</b>
Zhang, Sigong	<b>ICW-B5-5</b>
Zhang, Xiangmei	ICW-B6-6
Zhang, Yue	ICW-B5-1, ICW-B5-2
Zhao, Jidong	ICW-B1-3
Zhao, Jiuliang	ICW-C7-6, ICW-B8-6
Zhao, Yan	ICW-C7-6
Zoshima, Takeshi	<b>W4-2</b> , W33-4, <b>W44-6</b> , W60-3, P1-209, P1-242, P2-120, P3-192
Zukawa, Mineyuki	<b>P3-132</b>
Zwillich, Samuel H	W15-1, W15-2, W15-3

---

---

## **Modern Rheumatology Abstract Supplement**

The 59th Annual Scientific Meeting

JCR2015 Annual Course Lecture

---

**Publishing date: March 24, 2015**

**Publishers: Japan College of Rheumatology (JCR)  
Modern Rheumatology Editorial Board**

Okamotoya 2nd Bldg. 9F

1-22-16 Toranomom, Minato-ku,

Tokyo 105-0001, Japan

Tel. +81-3-5251-5353, Fax. +81-3-5251-5354

URL: <http://eng.ryumachi-jp.com>

E-mail: [MR@ryumachi-jp.com](mailto:MR@ryumachi-jp.com)

### **Production**

Hidejima Inc.

Toshin Nishi-Shinjuku Bldg. 2F

7-18-16 Nishi-Shinjuku, Shinjuku-Ku, Tokyo, 160-0023, Japan

Tel. +81-3-5331-3170, Fax. +81-3-5331-3171

E-mail: [gakkai@hidejima.co.jp](mailto:gakkai@hidejima.co.jp)

---

---

*Copyright ©2015 by Japan College of Rheumatology*

<http://eng.ryumachi-jp.com/journals/index.html>